

When systemic lupus erythematosus (SLE) involves pain: occurrence and impact on daily life

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Institutet**

Stockholm 2018

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Published by Karolinska Institutet.

Printed by Arkitektkopia AB

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ISBN 978-91-7831-294-8

When systemic lupus erythematosus (SLE) involves pain: occurrence and impact on daily life

THESIS FOR DOCTORAL DEGREE (Ph.D.)

by

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To my mother who was in my mind throughout this work. I miss you.

ABSTRACT

Living with a rheumatic disease, such as systemic lupus erythematosus (SLE), can pose many challenges. SLE is commonly considered to be a chronic disease, often occurring in unpredictable flares with alternating low and high disease activity. The disease predominantly affects women, but incidence and prevalence differ across different populations. SLE may potentially affect most organ systems with corresponding subjective symptoms, as well as objective signs. In general, pain is a commonly reported symptom in patients with SLE. Other common symptoms are fatigue, anxiety and depression. Patients with SLE are also reported to have a poorer health-related quality of life (HRQoL) compared to the general population. All these factors constitute a potential risk for impairment of health as well as a negative impact on daily life. Even though there is no cure for SLE, modified treatment regimens and new, potentially active drugs have been developed in recent decades. However, previous studies have shown that patients consider SLE-related pain not to be sufficiently addressed by healthcare providers. Even considering modified treatment regimens, the heterogenous nature of SLE, as well as new findings on pain mechanisms, the question of whether SLE-related pain is still common and constitutes a health barrier remains unanswered. As far as we know, no studies have been conducted in recent years in which HRQoL, fatigue, anxiety, and depression have been investigated from a pain and degree of pain perspective. More detailed knowledge on extent, intensity and characteristics is therefore required. In addition, the chronic course of SLE underlines the importance of investigating how SLE-related pain varies over time, and the patient's experience of how healthcare providers address SLE-related pain.

Aim: The aims of this thesis were to explore to what extent patients with SLE report disease-related pain and how pain relates to HRQoL, fatigue, anxiety and depression, as well as to disease duration, disease activity and damage. The aim also included investigation of how the pain varies over time and impacts on daily life.

Method: Data were collected from two cross-sectional cohort studies at inclusion (year 0) and seven-year follow up (year 7). At year 0, 84 patients with SLE and 91 age- and sex-matched controls from the general population completed self-assessment measures and questionnaires on pain using the Visual Analogue Scale (VAS) and the short-form McGill Pain Questionnaire (SF-MPQ); fatigue using the Multidimensional Assessment of Fatigue (MAF); HRQoL using the Medical Outcomes Survey-Short Form 36 (SF-36); and anxiety and depression using the Hospital Anxiety and Depression Scale (HADS). These assessments and questionnaires were completed again at year 7, when 64 of 84 patients with SLE and 68 of 91 gender- and age-matched controls from the inclusion cohort participated. In addition,

data on age, disease duration, disease activity and damage, as well as treatment with glucocorticoids were collected at both years 0 and 7. At year 7, data collection was supplemented with assessment of pain-related problems (VAS), data on pain duration, a pain drawing, and data on analgesics. At year 0, the patients were dichotomized into two groups designated the low-pain group and the high-pain group based on their SLE-related pain intensity score using VAS. A cut-off value, 40 millimetres, was chosen based on the distribution of scores using VAS. The division into the low-pain group and the high-pain group at year 0 was used for intra-group comparisons of collected data at both year 0 and year 7.

A qualitative approach was applied to investigate the impact of SLE-related pain on health and daily life, as well as the patient's expectations of healthcare providers. Twenty patients from two cohorts in the same urban region, south and north, participated in an interview study. The recorded interviews were based on an interview guide and transcribed verbatim. Thereafter, the text was analysed using qualitative content analysis.

Results: At year 0, the patients in the high-pain group constituted 24% of the SLE cohort and were characterized by significantly shorter disease duration and higher disease activity compared to the patients in the low-pain group. The patients in the high-pain group used significantly more descriptive words compared to the patients in the low-pain group when scoring their pain intensity using SF-MPQ. They also reported significantly lower HRQoL and scored higher levels of fatigue, anxiety and depression compared to the patients in the low-pain group and the controls. However, the low-pain group did not differ significantly from the controls regarding reported pain, fatigue, anxiety and depression. Treatment with glucocorticoids did not differ between the pain subgroups, and patients treated or not treated with glucocorticoids did not differ when scoring pain intensity. At follow-up in year 7, the high-pain group scored significantly lower levels of SLE-related pain using VAS. However, only half of the patients in the high-pain group scored a lower pain intensity while the other half had an unchanged pain score level from year 0. These patients with remaining high pain level scored statistically similar levels for HRQoL (except for a poorer score for the dimension vitality), as well as for fatigue, anxiety and depression as year 0, and significantly poorer scores in all self-reported assessments except for anxiety (HADS) and mental health (SF-36), compared to the patients with decreased pain, the low-pain group and the controls at year 7. Conversely, the patients with decreased pain scored significant improvements in all self-reported assessments. The patients in the low-pain group scored statistically similar levels for pain, most dimensions of HRQoL (SF-36), as well as for fatigue, anxiety and depression at year 7 as at year 0. Further, the patients in the low-pain group scored mainly

statistically similar levels as the controls and the patients with decreased pain at year 7.

In the interview study, the informants delineated their disease-related pain as long-standing, unpredictable and migratory. They also depicted a high symptom burden from their disease-related pain on health and daily life. The informants used several strategies to deal with pain, mainly through adaption and by finding new ways to perform different tasks and to maintain their roles in relation to others. They expected their pain to be acknowledged and to be met well by the healthcare providers. Furthermore, interventions against pain which were not dependent on economic prerequisites, and individual tailored advice and information were also requested.

Conclusion: Taken together, the results from these studies revealed that severe SLE-related pain (≥ 40 mm on VAS) is present in a minority of the patients with SLE. Furthermore, the pain intensity tended to decrease over time. Despite that, the patients with remaining severe pain reported a high symptom burden with impaired HRQoL, more fatigue, anxiety and depression, even though mental health appeared to be less affected. In spite of the fact that patients with severe pain use several strategies to deal with pain, individual adapted interventions designed to alleviate pain and support for the patients are strongly needed from healthcare providers. Moreover, acknowledgement of SLE-related pain is crucial.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers, which will be referred to by their Roman numerals throughout the thesis.

- I. **Waldheim, E.**, Elkan, A.C., Bergman, S., Frostegård, J., van Vollenhoven, R., Welin Henriksson, E. Extent and characteristics of self-reported pain in patients with systemic lupus erythematosus
Lupus (2013) 22; 136-143
- II. **Waldheim, E.**, Elkan, A.C., Pettersson, S., van Vollenhoven, R., Bergman, S., Frostegård, J., Welin Henriksson, E. Health-related quality of life, fatigue and mood in patients with SLE and high levels of pain compared to controls and patients with low levels of pain
Lupus (2013) 22; 1118-1127
- III. **Waldheim, E.**, Ajeganova, S., Bergman, S., Frostegård, J., Welin, E. Variation in pain related to systemic lupus erythematosus (SLE): a 7-year follow-up study
Clinical Rheumatology (2018) 37; 1825-1834
- IV. **Waldheim, E.**, Pettersson, S., Bergman, S., Welin, E. The implications of pain in systemic lupus erythematosus (SLE): the patient's perspective
Manuscript

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
CWP	Chronic Widespread Pain
DMARD	Disease Modifying Anti Rheumatic Drug
GFI	Global Fatigue Index
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-Related Quality of Life
IQR	Interquartile Range
MAF	Multidimensional Assessment of Fatigue
SF-36	Medical Outcomes Survey-Short Form 36
SF-MPQ	Short-Form McGill Pain Questionnaire
SLAM	Systemic Lupus Activity Measure
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLEVIC	SLE Vascular Impact Cohort
SLICC	Systemic Lupus International Collaborating Clinics
VAS	Visual Analogue Scale

1 FOREWORD

Taking part of patients' experiences of pain from different rheumatological diseases, in particular patients with systemic lupus erythematosus (SLE), is common in my long career as a nurse in rheumatology care. Gratifyingly, pharmacological advances in recent decades have made it possible to reduce disease activity and thereby reduce pain. However, despite these advances, some patients still express pain. Interventions and pharmacological treatments to reduce pain are not as well developed as for organ manifestations and, because there is no obvious life-threatening organ manifestation, patients with pain are often considered to have a mild disease. However, from my perspective as a nurse, for whom health is of central importance, SLE-related pain poses a risk of being a health barrier. Due to organizational structures and the complex nature of SLE, these patients are also at risk of being passed from one healthcare provider to another, which can add to the existing burden of a chronic disease. Thus, when an opportunity appeared to further investigate the experience of pain in patients with SLE, I wanted to find out whether I could confirm my concerns regarding impaired health in patients with SLE-related pain. Furthermore, I wanted to find out what patients with SLE-related pain thought they needed to deal with pain.

Hopefully, the results from this thesis will constitute a base for further research on supporting patients in dealing with SLE-related pain, and inspire the establishment of networks between healthcare providers for multidisciplinary care and interventions.

2 INTRODUCTION

Living with a chronic disease may pose many challenges for the patient especially in diseases with an unpredictable course such as systemic lupus erythematosus (SLE) (1). SLE is a systemic autoimmune rheumatic disease potentially affecting most organ systems by autoimmune inflammation, and displays a wide range of symptoms and severity depending on which organ is affected (2). Due to advances in medical care and treatment over recent decades, morbidity and mortality has decreased considerably and, generally, the disease is no longer considered life-threatening. However, the disease is still considered to be a chronic disease for which there is yet no cure.

Pain, which is the focus of this thesis, is described as a common and burdensome symptom in patients with SLE (3-5), and thereby may constitute a threat to health as defined in the World Health Organization (WHO) constitution (6) “health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity...”. This definition of health originates from 1948 and has later been supplemented to provide a more comprehensive definition. Notwithstanding, this original sentence introduces the definition of health that is used in this thesis.

In addition, despite advancement in medical care, reports exist where patients with SLE express dissatisfaction with how pain is met by healthcare providers (7, 8). Due to the heterogeneous nature of SLE, pain may compete with other concomitant symptoms, some of which are potentially life-threatening, for example lupus nephritis. Absence of serious internal organ involvement may cause the healthcare provider to perceive the disease as mild, and to underestimate and trivialize the patient’s experience of pain (8). Moreover, feelings of not being understood and not being taken seriously may create a lack of dignity and suffering, adding to the already existing burden of a chronic disease (9).

From a nursing perspective, health is of central importance. For example, health is present in the nursing metaparadigm: health, person, environment and nursing (10). Moreover, promoting and restoring health are areas of responsibility in nursing according to the International Council of Nurses (ICN) (11). Thus, due to the prolonged course of the disease, efforts should be made to support patients with SLE and pain to experience health.

Investigating patients’ experiences of SLE-related pain and how pain affects their lives is of crucial importance. The results will contribute to an updated and extended knowledge and point out which interventions and further research are needed to support patients with SLE to improve and maintain health.

3 BACKGROUND

3.1 SYSTEMIC LUPUS ERYTHEMATOSUS AND IMPACT ON LIFE

Systemic lupus erythematosus (SLE) is a systemic autoimmune rheumatic disease characterized by changes in the immune system and expression of autoantibodies mainly against components in the nucleus, such as the antinuclear antibodies (ANA), which include subgroups even more specific for SLE. Typically, the disease has a flare pattern with periods of low disease activity which switch to periods of high disease activity. The cause of the disease is not yet fully understood, but it is known that both genetics as well as environmental factors contribute to the development of the disease. Exposure to UV light is a well-known environmental factor, but virus infections and pharmaceuticals are also suspected to be triggering factors (12). The disease is considered rather uncommon, and prevalence and incidence vary between studies and populations. The estimated annual incidence rate for Europe is between 1 and 4.9 per 100,000 and the annual worldwide incidence rate ranges from 1 to 8.7 per 100,000. The prevalence in Europe ranges from 28 to 97 per 100,000 and worldwide from 28.3 to 149.5 per 100 000 (2, 13, 14). SLE is more common in females than men in an approximate 9:1 ratio, which suggests female hormones could be triggers for developing the disease (2).

Commonly affected organs are the joints and the skin but basically all organs can be affected by the inflammation. Feared manifestations include inflammation in the central nervous system and nephritis. The severity of the disease varies widely from very mild to severe. The disease was previously considered to be life-threatening, but newer treatment regimens and pharmaceuticals have resulted in decreased morbidity and mortality. However, mortality is still higher compared to the general population, and is also associated with a higher risk of cardiovascular disease (2).

In addition to organ-specific symptoms, common patient-reported symptoms are fatigue, pain, malaise and fever (2).

Disease-specific criteria have been developed to identify patients with SLE, especially in research settings. The first criteria were developed in 1971 by the American College of Rheumatology (ACR) and were revised in 1982 and 1997. The most recent version of the criteria was developed in 2012 by the Systemic Lupus International Collaborating Clinics (SLICC). The revised versions reflect the difficulty in comprehending the heterogeneous nature of SLE, as well as new knowledge in immunology and new understanding of the results of serological tests (15). The criteria from 1982 from the American College of

Rheumatology (ACR) have been validated and are commonly used (16). To meet these criteria in a research setting, four out of eleven criteria must be met (Table 1).

Table 1. 1982 revised ACR criteria for identification of patients with SLE in clinical studies; 4 or more of 11 manifestations should be present (16)

Malar rash	Renal disorder
Discoid rash	Neurological disorder
Photosensitivity	Haematological disorder
Oral ulcers	Immunological disorder
Arthritis	Antinuclear antibody (ANA)
Serositis	

Similarly to other patient groups with longstanding diseases, patients with SLE must deal with many challenges, and are at risk of a negative impact on daily life and health. However, SLE can exhibit varying degrees of symptoms and severity, and thus affect individuals in very different ways. In general, earlier studies showed poorer health-related quality of life, more fatigue and pain as well as more symptoms of anxiety and depression in patients with SLE compared to controls (2, 17-21). Moreover, earlier studies showed a negative impact on various aspects of life for patients with SLE such as difficulties in relationships with family, spouses and others, impaired working ability in and outside the home, with a consequent negative economic impact, and negative self-perception (22-26). Pharmacological treatment to reduce disease activity, which comprises immunosuppressive drugs including glucocorticoids and biologics (2), offers opportunities but can also lead to patient-reported concerns about toxicity and side effects (22). In interview studies (22, 27), patients with SLE have described the uncertainty that resulted from the unpredictable course and fluctuating activity of the disease. However, the patients who were interviewed also learned to manage the disease and its symptoms and found potential in their lives.

Previous studies have reported mutual relationships between commonly self-reported symptoms such as pain, fatigue, anxiety and depression and those symptoms relationship with HRQoL (4, 28-31). There are also reports that patients with SLE experience dissatisfaction concerning help with these symptoms from healthcare providers (7, 8, 32).

3.2 PAIN

Pain is a subjective sensation defined by the International Association for the Study of Pain (IASP) as “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”(33). The definition highlights the complex nature of pain and the multidimensional influence it may have on the individual. Nevertheless, pain is not only negative - it is also essential in defending the body against potentially threatening inflammation and damage (34).

Pain can be classified from different perspectives (35):

- **Intensity:** mild, moderate and severe pain
- **Duration:** acute, long-standing, transient and breakthrough pain
- **Origin:** postoperative/post-traumatic pain, cancer-related pain, long-standing pain
- **Aetiology:** physiological pain, physiological inflammatory pain, pathological inflammatory pain (nociceptive pain) neuropathic pain and somatic pain

Nociceptive pain is generated by noxious stimulation of nociceptors located in peripheral nerve endings in cases of injury and/or inflammation. The nociceptors transmit signals from damaged tissue via action potentials to the central nervous system through the dorsal root ganglia (36). Neuropathic pain arises from injury or disease in a peripheral or central nerve, for instance pain after stroke or postherpetic neuralgia (37). The conscious perception of pain emerges through processing pain stimulus in a network of different areas in the brain commonly called the pain neuromatrix (34).

Long-standing pain is defined as pain that persists beyond the expected healing time or more than three months (38). The prevalence of long-standing pain in European adults in the general population ranges from 19 to 53% (39-41). Chronic widespread pain (CWP) is defined by the sub-criteria as a part of the ACR 1990 criteria for fibromyalgia syndrome as suggested by Wolf et al. (42), “persistent pain for more than three months and pain in both sides of the body, pain over and below the waist and axial pain (cervical and thoracic spine, anterior chest pain and low back pain) must be present. In this definition, left or right shoulder and buttock pain were considered as pain for each involved side”.

Persistent pain after expected healing time and pain without any obvious stimulus is considered to be a disease in the peripheral and/or central nervous system (34). Central sensitization denotes a condition with disturbances in normal pain processing in the central nervous system with increased activity in the pain facilitation pathways, together with disturbed function in the descending inhibitory pathways and overactivity in the pain

neuromatrix. Central sensitization is characterized by generalized hypersensitivity and/or allodynia, which refers to pain triggered by stimulus that usually do not trigger pain (43).

The treatment of pain in different conditions with long-standing pain and persistent pain due to central sensitization is primarily multidisciplinary. Non-pharmacological treatment constitutes the cornerstone in reducing/alleviating pain in long-standing musculoskeletal pain. Studies on non-pharmacological treatments include cognitive behavioural therapy (CBT), acceptance and commitment therapy (ACT), physical activity/exercise, patient education (in group or individual), as well as complementary alternative medicine (CAM; acupuncture, massage, yoga). In addition, pharmacological treatment such as analgesics, antidepressants and anticonvulsants may be beneficial. The majority of non-pharmacological treatments usually provide beneficial outcomes when used in combination with pharmacological treatment (40, 44).

Pain is a prominent symptom in several rheumatic diseases and current research indicates that repeated stimulation of peripheral nociceptors, as in inflammation, may cause functional and structural changes in the central nervous system leading to abnormal pain processing, such as central sensitization (45, 46).

3.3 PAIN IN PATIENTS WITH SLE

Although not all patients with SLE report pain (3), it is a common self-reported symptom, and one of the most common symptoms in the early stage of the disease and before diagnosis (4, 47, 48).

The most common locations for SLE-related pain are the musculoskeletal system in terms of arthralgia, arthritis and myalgia, but headache and Raynaud's phenomenon are also commonly present (3, 47). During the course of the disease, musculoskeletal pain is reported to be present in 50% to 90% of patients with SLE (4, 49). Pain related to SLE has been described by the patients as obtrusive and unpredictable, sometimes with a continuous nature but also with rapid changes in intensity and location (27). The cause and pathophysiology of pain in SLE may vary and is not always evident. Theoretically, pain in SLE can be explained by inflammatory, neuropathic and central pain (5). The most common type of pain in SLE is reported to be inflammatory (nociceptive) pain, mainly in the joints. Neuropathic pain in SLE includes peripheral neuropathic pain in terms of neuropathies and neuropathic pain in the central nervous system. The underlying cause of neuropathic pain in the central nervous system, with symptoms of headache and neuropsychiatric SLE, remains unclear (49). Central pain refers to disturbed pain processing in the central nervous system, usually called central

sensitization as described previously (5, 49), which is believed to be the underlying cause of chronic widespread pain (CWP). CWP constitutes the core of the criteria for fibromyalgia syndrome (42) and is highly prevalent in patients with SLE, range 65% to 80% (49).

Likewise, concomitant fibromyalgia syndrome is common and, although varying between different studies, the prevalence is reported to be 17% to 40% in patients with SLE (47, 50). There are several common and overlapping symptoms in SLE and fibromyalgia syndrome such as pain and fatigue. These similarities may affect and confound diagnostic assessment and lead to under- and over-diagnosis of fibromyalgia syndrome and SLE, respectively (50). The similarity between SLE and fibromyalgia syndrome may also impact and confound the selection of treatment. Since there are different treatment regimens in different pain conditions and in SLE, determining the cause of pain in patients with SLE appears crucial to avoid an incorrect diagnosis as well as over- and undertreatment (5).

Except for pharmacologic analgesia, treatment interventions for SLE-related pain have been sparsely investigated. However, there are a few, including a pilot, randomized controlled study which demonstrated a beneficial effect of acupuncture (51). Further, an intervention study based on a Problem-based learning (PBL) programme was demonstrated to be beneficial in improving self-care empowerment in patients with different rheumatic diseases and chronic musculoskeletal pain (52).

Although many patients with SLE cope well with disease-related pain, it has been identified by patients to be a health problem (3, 48) where pain impairs HRQoL, reinforces the effect of fatigue and has a complex impact on the psychological state (28-31).

Moreover, pain in SLE may contribute to limitations in daily activities like exercise, household chores, gardening, and even occasionally personal hygiene (22, 23, 53-55). SLE-related pain is also associated with work disability and high absence from work (24).

Patients with SLE have also expressed dissatisfaction with how pain in SLE is met and acknowledged by healthcare providers (7, 32, 56).

3.4 HEALTH, QUALITY OF LIFE AND HEALTH-RELATED QUALITY OF LIFE

A common definition of health is that by the WHO (6), “health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity..”. In addition, health can be seen as a continuum with two extremes, illness and health, where the person makes transitions along the continuum (57). To experience health does not necessarily exclude disease and disease does not always mean experiencing illness (58).

There are several definitions of the concept quality of life (QoL) based on different perspectives (59). Although, there is no clear consensus on how to define the concept, there is agreement that the concept is multidimensional (60). QoL is frequently used as an outcome variable not only in nursing but also in medical, social, economic and behavioural research (60). The WHO defines quality of life as “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad-ranging concept affected in a complex way by the person’s physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment” (61). QoL could be difficult to distinguish from the concept health which is also a multidimensional concept most commonly defined by the WHO as cited earlier. However, it is deemed that there is a clear distinction between the two concepts where the definition of quality of life is broader, and the concepts cannot be used interchangeably (62). Smith et al. (62) found in a meta-analysis that patients considered mental health when rating quality of life but physical function when rating health status. However, Plummer and Molzhan (59) found the concepts QoL and health so alike and so closely related that they proposed that QoL could replace health in the nursing metaparadigm.

Health-related quality of life denotes QoL in connection with health and narrows the broader definition of QoL (63).

3.5 HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH SLE

In earlier reviews, health-related quality of life (HRQoL) in patients with SLE is reported to be poorer compared to controls and population norms regardless of measurement and population under study. However, studies show that different dimensions of HRQoL seemed to be more or less affected by SLE in different studies (17, 18, 64, 65).

There are conflicting results regarding the relationship between HRQoL, disease activity and damage. Nevertheless, most studies found no obvious relationship between HRQoL, disease activity and damage (17, 18, 66) which may indicate a complex relationship with influencing factors that are difficult to sort out.

Several factors have been shown to potentially influence HRQoL in patients with SLE; the disease itself, treatment and the patient’s ability to cope with the disease. Factors identified to promote HRQoL in patients with different rheumatic diseases include support from significant others, sleeping well and feeling well-rested, a strong sense of coherence, being

young or middle-aged and being able to work (67, 68). In addition, a decrease in SLE-related pain and feeling pain-free have been shown to improve HRQoL (67, 69).

3.6 FATIGUE IN PATIENTS WITH SLE

Commonly, fatigue is described as uncontrolled, untreatable physical and mental exhaustion, not synonymous with tiredness (70). Fatigue is a frequently self-reported symptom in patients with rheumatic diseases, particularly in SLE, and is often described as a paramount subjective symptom (2, 4, 20, 71). Approximately 53% to 80% of patients with SLE report fatigue as one of their primary symptoms (72). SLE-related fatigue is described by patients as controlling, unbeatable and beyond words, and fatigue and pain have been reported to reinforce each other (28, 71, 72). Fatigue in SLE is reported to have a considerable negative impact on several dimensions of daily life such as work, practical daily activities, leisure, social and family activities as well as negative emotional and cognitive impacts (73).

The cause of fatigue in SLE is not clear but likely multifactorial (72) where mechanisms in the peripheral and central nervous system contribute (74). Elevated levels of IL-1 β in cerebrospinal fluid have been found in patients with rheumatoid arthritis compared to controls (75), and where elevated levels of IL-1 β correlated with assessment of fatigue but not with assessment of pain and tender joints (76). Convincing evidence for interventions aimed at reducing fatigue in SLE is lacking. However, there are indications that aerobic exercise and belimumab may be effective (77). Currently, more knowledge is needed to understand and develop further interventions to reduce and alleviate fatigue in SLE and other inflammatory diseases.

Taken together, the great impact of SLE-related fatigue on daily life implies that fatigue can be considered as a potential health barrier.

3.7 ANXIETY AND DEPRESSION IN PATIENTS WITH SLE

Anxiety and depression are reported to be more prevalent in patients with SLE compared to the general population (19, 20), and present in 28% to 65% of the patients (19, 75, 78). However, the prevalence varies between studies and probably due to the method and assessment used (21). The mechanisms behind these common symptoms as well as other psychiatric and neuropsychiatric symptoms in patients with SLE are unclear, but a number of theories exist (79). Self-reported disease activity (19) emerged as one of the theories on causes and contributing factors, and another theory suggested a reaction to living with an unpredictable chronic disease with poor understanding of the disease (80). Kozora et al. (20) found a strong correlation between cognitive impairment and depression, pain and fatigue in patients with

neuropsychiatric SLE and therefore suggested global changes in the central nervous system. Psychiatric symptoms in patients with SLE, especially anxiety and depression, are known barriers to having a good HRQoL (18).

The complex relationship between pain, fatigue, anxiety and depression and the role of pain as a barrier to reach health is presented in Figure 1.

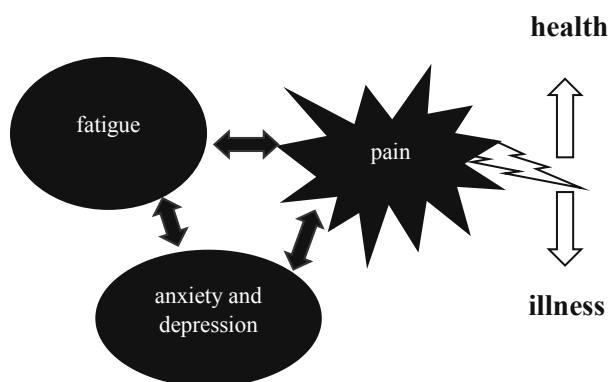


Figure 1. The complex relationship between pain, fatigue, anxiety and depression and pain as a barrier to reach health

4 RATIONALE FOR THE THESIS AND AIMS

Over the last decades there have been advances in medical care and pharmacological treatment for patients with SLE, leading to decreased morbidity and mortality. In addition, there are new insights into pain and pain-processing mechanisms. Despite these advances, some previous studies report that pain in SLE is still a common self-reported symptom (4, 8, 47) and may constitute a threat to health (3, 48). In addition, some studies report a mutual relationship between pain and other subjective symptoms such as fatigue, anxiety and depression, and that patients with SLE experience that healthcare providers pay insufficient attention to these subjective symptoms (7, 8, 32, 56). In respect of these previous studies, more detailed knowledge on the occurrence, intensity and characteristics of self-reported SLE-related pain is needed. The chronic nature of SLE makes it important to investigate how pain varies over time, how pain relates to fatigue, anxiety and depression over time, as well as how pain affects HRQoL and different aspects of daily life. Since pain is reported to be a common symptom in the general population (39, 40), the studies also investigate whether there are any differences in reported pain between patients with SLE and controls from the general population. Furthermore, an update is needed on how patients with SLE experience how healthcare providers address SLE-related pain, and what they believe they need from healthcare providers to better deal with the pain.

The overall aim of this thesis was to explore to what extent patients with SLE report disease-related pain and how pain influences health and different aspects of life.

The aim of study I was:

- to investigate the extent of self-reported SLE-related pain in terms of intensity and characteristics
- to measure disease activity and disease duration in relationship to pain

The aim of study II was:

- to investigate overall pain, health-related quality of life, fatigue, anxiety and depression in patients with SLE and age- and sex-matched controls from the general population

The aim of study III was:

- to investigate self-reported SLE-related pain in a seven-year follow-up survey, as well as the presence of long-standing widespread pain, health-related quality of life, fatigue, anxiety and depression

The aim of study IV was:

- to acquire a deeper understanding of what SLE-related pain means to the patients in daily life and what support is needed from healthcare providers to deal with SLE-related pain

5 STUDY POPULATION AND METHODS

Both a quantitative and a qualitative approach were applied in this thesis. Initially, two quantitative cross-sectional studies were performed to investigate the existence of pain and its connection with HRQoL, fatigue, anxiety and depression (inclusion, year 0). These studies were followed by a quantitative cross-sectional seven-year follow-up study (year 7) of the same cohort and with patient reported assessments and questionnaires. In addition, a qualitative interview study was performed to obtain a deeper insight into the patients' experiences of SLE-related pain and how pain influences daily life, data which are difficult to gain through quantitative methods.

5.1 STUDIES I-II

The participants in the inclusion study (year 0) were recruited consecutively from an on-going cohort study, SLEVIC (SLE Vascular Impact Cohort) (81), in which patients with SLE according to the 1982 revised ACR criteria (16), aged 18 to 70 years, participated. Potential study participants for the cohort study were identified by diagnosis codes in the electronic medical record system at the Department of Rheumatology, Karolinska University Hospital, Huddinge, Stockholm, Sweden. Identified potential study participants were mailed letters with an invitation to participate in the cohort study. They were also invited by telephone and in connection with routine visits at the clinic. For comparison, sex- and age-matched controls were randomly identified from the general population through the Swedish population register. These controls were from the same greater urban area as the patients and were invited to participate in the cohort study by mail.

Over a period of 13 months, from 2006 to 2008, 84 patients and 91 controls from the ongoing cohort study were invited to participate in the present inclusion study. All agreed to participate.

5.2 STUDY III

In the seven-year follow-up study (year 7) performed from 2013 to 2015, it was possible to follow 64 (76%) of 84 patients and 68 (75%) of 91 controls recruited from the original inclusion study (year 0). Reasons for not participating in the follow-up study for the patients were: death (n=4), migration (n=3), unable to participate due to illness other than SLE (n= 2) and unwilling to participate (n=11); and for the controls: migration (n=1), unable to participate due to illness (n=5) and unwilling to participate (n=17). No significant difference in age (years) was found between those patients who participated, median interquartile range (IQR) 52 (38.5 to 64) and those who did not, 54.3 (45 to 64.6) (p=0.29), nor for the controls

who participated, 56 (46.5 to 66) and those who did not, 49.7 (38.2 to 67.5) ($p=0.15$). Furthermore, there was no significant difference in disease duration (years) among those patients who participated, median (IQR) 16 (11.5 to 22.5) and those who did not 16 (13 to 25) ($p=0.74$) in the seven-year follow-up study.

5.3 STUDY IV

In connection with the self-assessment questionnaires at the seven-year follow-up study, the patients were asked whether they were interested in participating in a subsequent interview study on SLE-related pain. The response options were *yes*, *no* and *maybe*. All patients in the follow-up study who had ever reported SLE-related pain during the previous week ≥ 40 mm on VAS, either at inclusion or at follow-up or at both, and who had responded *yes* or *maybe* to the question regarding participation in the interview study, were invited by phone to participate in the interview study. Of 20 potential participants, 12 (60%) patients agreed to participate. For a suitable sample of informants, another eight participants who had reported SLE-related pain during the previous week ≥ 40 mm on VAS were recruited. This enabled patients to participate both from the north and south within the same urban area.

The studies, designs and populations are summarized in Table 2 and demographics and characteristics of the study populations are presented in Table 3.

Table 2. Summary of the four studies; participants, design, outcome measures and analysis

Name of the study		Participants, n	Design	Outcome measures	Analysis
I	Extent and characteristics of self-reported pain in patients with systemic lupus erythematosus <i>Lupus (2013) 22; 136-143</i>	84 patients ^a 91 controls	quantitative self-assessment questionnaires	VAS, pain 100 mm SF-MPQ disease duration disease activity and damage	descriptive statistics: Chi ² /Fischer's exact test, Sign Test, Mann-Whitney U Test, Spearman's Rank Correlation Coefficient (r)
	Health-related quality of life, fatigue and mood in patients with SLE and high levels of pain compared to controls and patients with low levels of pain <i>Lupus (2013) 22; 1118-1127</i>	84 patients ^a 91 controls	quantitative self-assessment questionnaires	VAS, pain 100 mm SF-36 MAF HADS	descriptive statistics: Sign Test, Mann-Whitney U Test
III	Variation in pain related to systemic lupus erythematosus (SLE): a 7-year follow-up study <i>Clinical Rheumatology (2018) 37; 1825-1834</i>	64 patients ^a 68 controls	quantitative self-assessment questionnaires	VAS, pain, 100 mm/problems, 100mm SF-MPQ SF-36 MAF HADS	descriptive statistics: Mann-Whitney U Test, Wilcoxon matched pairs test
	The implications of pain in systemic lupus erythematosus (SLE): the patient's perspective <i>Manuscript</i>	12 patients ^a 8 patients ^b	qualitative interviews	duration of pain and pain drawing disease duration disease activity and damage	qualitative content analysis

^apatients from the south of the urban area, ^bpatients from the north of the urban area, VAS= Visual Analogue Scale, SF-MPQ=Short-Form McGill Pain Questionnaire, SF-36= Medical Outcomes Survey-Short Form 36medical, MAF=Multidimensional Assessment of Fatigue, HADS=Hospital Anxiety and Depression Scale

Table 3. Characteristics of the patient cohort and controls from the general population in the studies of this thesis

	Studies I-II, n=84	Study III, n=64	Study IV, n=20	Study II, n=91	Study III, n=68
	Patients	Patients	Patients	Controls	Controls
Female ^a	72/86%	55/86%	19/95%	78/86%	58/85%
Male ^a	12/14%	9/14%	1/5%	13/14%	10/15%
Age, yrs ^b	45.9 (32.7 to 57)	52(38.5 to 64)	55.5 (43.5 to 68)	48.1 (34.1 to 59.7)	56 (46.5 to 66)
Disease duration, yrs ^b	9 (5 to 16)	16 (11.5 to 22.5)	18.8 (12.5 to 28.5)	nm	nm
Current treatment with oral glucocorticoids ^a	53/63%	34/53%	nm	nm	nm
Current dose of oral glucocorticoids, mg/day ^b	3.8 (0 to 7.5)	2.5 (0 to 5)	nm	nm	nm
Use of analgesic, regular ^a	nm	19/30%		nm	nm
Use of analgesic, as needed ^a	nm	23/36%		nm	nm
No use of analgesics ^a	nm	22/34%		nm	nm
SLICC ^b	1 (0 to 3)	1 (0 to 3)	nm	nm	nm
SLEDAI ^b	3 (0 to 6)	nm		nm	nm
SLEDAI-no lab ^b	1 (0 to 4)	0 (0 to 3)	nm	nm	nm
SLAM ^b	6 (4 to 10)	nm	nm	nm	nm
SLAM-no lab ^b	6 (4 to 9)	5 (3 to 7)		nm	nm

^a numbers (%), ^bmedian with interquartile range (IQR), nm=not measured, SLEDAI-no lab=SLEDAI without complement and ds-DNA, SLAM-no lab=SLAM without lymphocytes

6 DATA COLLECTION

In studies I-III, the participants were invited to respond to self-assessment questionnaires on pain, HRQoL, fatigue, anxiety and depression in connection with the inclusion visit in the cohort study and the seven-year follow-up visit (Table 2). In addition to the self-assessment questionnaires, characteristics such as age, disease duration, disease activity and damage, current treatment with glucocorticoids and disease modifying anti-rheumatic drugs (DMARD) were collected. At the seven-year follow-up study (study III) the participants were also asked to report current use of analgesics if applicable.

Studies I-III were conducted at an outpatient clinic in the Rheumatology Department at the Karolinska University Hospital, Huddinge, Stockholm, Sweden. In Study IV, the interview was conducted at a location chosen by the informant.

6.1 SELF-ASSESSMENTS AND QUESTIONNAIRES

6.1.1 Pain

A visual analogue scale (VAS) was used to measure self-reported pain intensity during the previous week, (82, 83). The scale consists of a 100 millimetre (mm) long horizontal line symbolizing a continuum of increased pain with two extreme endpoints. The beginning of the line represents *no pain* and the end of the line represents *worst imaginable pain*. The scales were connected to the questions *how much pain have you experienced on average the last week?* and for the patients only *how much pain due to SLE have you experienced on average the last week?* The participants estimated their pain during the previous week by placing a transverse line on the 100 mm horizontal line. Cut-off values on VAS, e.g. for mild, moderate and severe pain, are not fully defined. Common cut-off values on VAS for patients with acute pain are 1 to 3 centimetres (cm) for mild pain, 4 to 6 cm for moderate pain and 7 to 10 cm for severe pain (84). Boonstra et al. (85) found that ≤ 3.4 cm best corresponded to mild pain, 3.4 to 7.4 cm to moderate pain and ≥ 7.5 cm to severe pain in patients with chronic musculoskeletal pain.

In order to measure the nature of self-reported pain, the short-form McGill Pain Questionnaire (SF-MPQ) (86) was also used. This form contains three items. In the first item the patients were asked to grade pain intensity (0=none, 1=mild, 2=moderate and 3=severe) for fifteen predefined descriptive words. The reported intensity of each descriptive word is thereafter summarized in a total index, range 0 to 45, where a higher score indicated more pain. Furthermore, the total index enables a score for sensory (0 to 33) and affective (0 to 12)

indices. In the second item, the patients were asked to report their current overall pain intensity using VAS. In the last and third item, the present pain index (PPI), the patients were asked to choose one of six predefined words that most accurately describes their present pain; *no pain, mild, discomforting, distressing, horrible* and *excruciating*. The form is considered to be suitable for use with patients with long-standing pain (84), and has been tested for validity and reliability in Swedish patients with fibromyalgia syndrome (87) and in Turkish patients with rheumatoid arthritis (88).

In addition to the VAS and the SF-MPQ, the participants were asked to respond to three additional self-assessments at the seven-year follow-up visit (study III); problems related to pain on VAS, duration of pain and if applicable a pain drawing (Table 2).

The VAS (100 mm) was connected to the question *to what extent has SLE-related pain been a problem for you over the previous week?*

To investigate the presence of CWP, the participants were also asked if their pain had lasted more than three months by choosing one of two response options, *yes* or *no*.

Those participants who reported pain lasting more than three months were asked to mark painful areas on a pain drawing with predefined body regions (89).

6.1.2 Health-related quality of life

To measure HRQoL in patients and controls, the Medical Outcomes Survey-Short Form 36 (SF-36) Standard Swedish Version 1.0 was used. The SF-36 is a generic instrument to measure the multidimensional concept of health in the general population and in other populations (90). It has been translated into Swedish and many other languages and cultural contexts (90). Although the instrument is generic, it can easily be supplemented with disease specific assessments. The SF-36 contains 36 items grouped into eight domains; *physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems* and *mental health*. Raw scores for each domain are transformed to a scale range 0 to 100, where 0 represent worst possible health state and 100 best possible health state. The psychometric tests of the Swedish version of SF-36 showed good validity and reliability (90, 91). The SF-36 has shown good validity and reliability in patients with SLE (65, 92-94), and is the most used HRQoL measure in patients with SLE and is recommended in clinical trials (17, 95). In a previous study (96), the SF-36 was shown to be sensitive to changes in terms of worsening and improvement in patients with active SLE.

6.1.3 Fatigue

To measure self-reported fatigue over the previous week in patients and controls, the Multidimensional Assessment of Fatigue (MAF) was used. The MAF contains 16 items symbolizing four dimensions of fatigue; severity, distress, degree of interference on daily activities and timing (when present and if any changes during the past week). In items 1 to 14, the respondents estimated severity and distress as well as the impact of fatigue on different activities in daily life from 1 to 10. In items 15 and 16, the participants estimated the overall frequency of fatigue and any changes during the past week using multiple choice responses. Items 1 to 15 can be used to calculate a global fatigue index (GFI) ranging from 1 to 50 where 1 represents no fatigue and 50 represents severe fatigue.

MAF has previously been used in patients with a number of different conditions and in different languages (97). Within rheumatology, the MAF has been used in patients with rheumatoid arthritis (98, 99), systemic sclerosis (100) and SLE (101). A recent review by Belza et al. (97) investigating the psychometric properties of MAF, showed that it exhibited high validity and reliability as well as good internal consistency in patients with different chronic diseases, including rheumatic diseases.

6.1.4 Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) (102) was used to measure anxiety and depression during the previous week in patients and controls. The measurement consists of seven questions concerning anxiety and seven questions concerning depression. Each question has four response options. The answers are summarized in two scales, anxiety (HADS-A) and depression (HADS-D) total index, which range from 0 to 21 where 0 represents no symptoms and 21 represents maximum distress. A score from 8 to 10 is defined as mild to moderate inconvenience, and a score above 10 justifies deeper diagnostics and possible treatment for both the anxiety and the depression total index.

The HADS has been tested in different contexts and in different populations; somatic, psychiatric and primary care patients, as well as in the general population (103). Strong validity and reliability have also been found in a Swedish population sample (104) as well as in a rheumatology setting (HADS-A) (105).

For an overview of the self-assessment questionnaires used in the studies, see Table 2.

6.2 DISEASE ACTIVITY AND DAMAGE

6.2.1 Disease activity

Disease activity was captured using the Systemic Lupus Activity Measure (SLAM) and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (95, 106) which are

physician-rated indices frequently used in research settings. Both SLAM and SLEDAI have been shown to be valid, reproducible and correlate well with other disease activity indices. SLAM measures signs and symptoms of the disease that have been present during the preceding month. Its score ranges from 0 to 84, and a score of seven or more is considered clinically important. SLEDAI measures medical signs from the disease during the previous 10 days. Its score ranges from 0 to 105. Score 0 indicates no disease activity, 1 to 5 indicate mild activity, 6 to 10 indicate moderate activity, 11-19 indicate high activity and ≥ 20 very high disease activity.

Both the physician and the patients scored global disease activity on VAS included in the SLAM, and the SLAM was also used to identify the most common location of pain in Study I (95).

6.2.2 Disease damage

Disease damage was captured using the physician-rated Systemic Lupus International Collaborating Clinics, American College of Rheumatology SLICC/ACR damage index (95). This index includes 41 items which cover 12 organ systems. Manifestations persisting continuously over six months after onset of SLE were recorded as damage, regardless of disease activity. SLE-specific co-morbidities as well as morbidity due to treatment for SLE are also included in the index. Score range 0 to 47.

The indices for disease activity and damage were captured by an experienced rheumatologist. As a supplement to measuring disease activity, the Erythrocyte Sedimentation Rate (ESR) according to the Westergren method was used (107). The ESR is also included in the SLAM. In Study III, disease activity was measured by SLAM without lymphocytes and SLEDAI without complements and antibodies to double-stranded DNA (ds-DNA).

6.3 INTERVIEWS

The interviews were conducted individually by the same interviewer (EWa) using an interview guide based on questions which emerged when the authors analysed data from the self-reported questionnaires. The interview guide consisted of seven main questions, mostly open-ended (Table 4). For clarification and a deeper understanding, these questions were followed by supplementary questions, if needed. The interviews were concluded with the question *do you want to tell us something more about your pain?*

A minor revision of the interview guide was made after a pilot interview with one of the controls who experienced pain.

Table 4. Main questions in the interview guide

How do you experience your pain?
Has the pain affected your relationships?
How does your pain affect your feelings of being ill?
How do you deal with pain?
Do you use any painkillers?
What support do you need from healthcare providers to better deal with pain?
Has the pain given you experiences that could mean something positive for you?

The interviews were recorded using a mobile phone and the average time for the interviews was 40 minutes. The recordings were then transcribed verbatim and all words and utterances were printed.

The participants were asked to choose what time and location they preferred for the interview. A secluded room in a care facility was offered, but the informants could also choose another location. Before any interview, a letter containing confirmation of the time and location was sent to the prospective informants. The letter also contained information that the interview would be recorded, that answering the questions was voluntary, and that the participant could discontinue the interview at any time.

7 DATA ANALYSIS

7.1.1 Statistics

In Studies I-III, the data were analysed using descriptive statistics. Due to a non-normal distribution of collected data, different group size and ordinal data, non-parametric statistics were used. The results were presented as the median and interquartile range (IQR). For comparative statistics between groups, Chi-squared/Fischer's exact test, the Sign Test, and the Mann-Whitney U Test were used. To compare paired data, Wilcoxon matched pairs test was used. Spearman's Rank Correlation Coefficient (r) was used for correlation analysis.

In Study III, the variation in self-reported pain was illustrated by calculating the difference between inclusion and the seven-year follow-up (inclusion minus follow-up). The difference represents an improvement if the difference consists of a positive number, except for SF-36 where higher values indicate better health.

A p-value less than 0.05 was considered statistically significant.

Power analysis was calculated post hoc in Study II, between the whole patient group and the controls, between the low-pain group and the high-pain group, and between the controls and the low- and high-pain groups, respectively (Table 5).

Non-parametric power was performed using the software nQuery Advisor 4.0 (Statistical Solutions, USA) and corresponding parametric power by STATISTICA 10 (Stat Soft Scandinavia AB, Uppsala, Sweden). Other statistical analyses were performed in STATISTICA 10 (Studies I and II) and 12 (Study III).

Table 5. Power calculation

	Patients versus controls		Low-pain group versus controls		High-pain group versus controls		Low-pain group versus high-pain group	
Sample size (n)	74	91	56	91	18	91	56	18
Power	0.63	0.72	0.08	0.10	0.99	0.99	0.99	0.99
Number of observations (in each group) to achieve a minimum power of 0.80	111		1362		7		6	
Number of observations (in each group) to achieve a minimum power of 0.90	148		1823		10		8	

7.1.2 Division into groups based on pain

When the intensity score for SLE-related pain the previous week on VAS (n=84) was analysed at inclusion (Study I), the median was 10.5 mm and the interquartile range (IQR) was 1 to 35.5 mm. Values above 40 mm constituted the scores beyond Q3 (>Q3) (Figure 2a). When dichotomized with the cut-off value of 40 mm, two groups appeared which did not overlap (Figure 2b). Thus, the cut-of value 40 mm, was chosen to divide the patients into two groups for comparative analyses. This cut-off value also coincides with the value often used to denote the threshold for moderate pain (84). The group scoring SLE-related pain 0-39 mm consisted of 64 patients and was named the low-pain group, and the group scoring 40-100 mm consisted of 20 patients and was named the high-pain group.

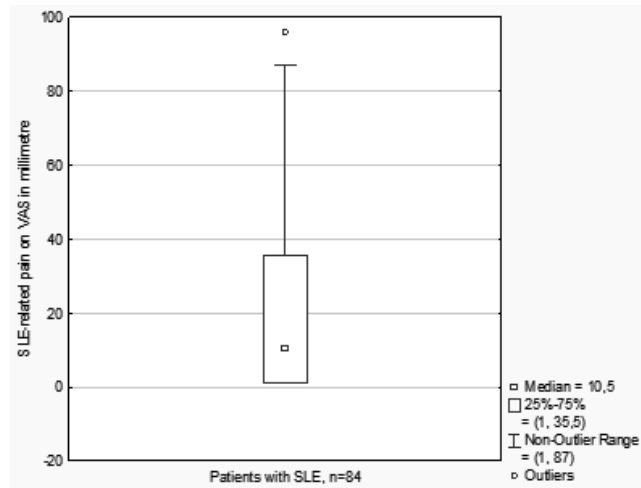


Figure 2a. Distribution of self-reported SLE-related pain

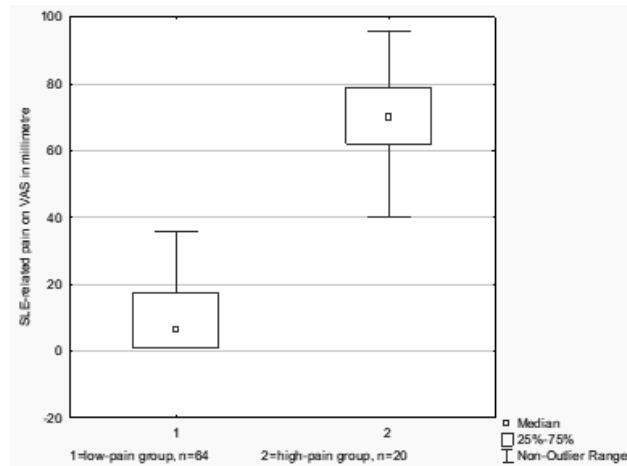


Figure 2b. Distribution of self-reported SLE-related pain on VAS in the low-pain group and in the high-pain group

This division into two groups was also used in Study II and maintained in the seven-year follow-up (Study III) where possible variations of SLE-related pain after seven years were investigated in each group.

7.1.3 Content analysis

In Study IV, the text from the verbatim transcribed interviews was analysed using content analysis and a classification scheme. Qualitative content analysis is a common research method for analysing data in terms of text in a structured manner based on its content or contextual meaning (108). The objective of qualitative research is not generalizability but transformability of the results from one context to another (109). To describe and understand

a subject, in the present study how the participants experience and manage SLE-related pain, a conventional approach was used. In the conventional content analysis, the codes and categories relevant for the purpose of the study emerge from the text data instead of predefined categories (108). The content of the text will thus be explored in an inductive way in which both the manifest and the latent content of the text may emerge (109-111).

7.1.3.1 Analysis process

The first step in the process was to read the entire text to acquire a sense of the whole (108, 111). In the second step, the text was inserted into the first column of the classification scheme, labelled *text*. Text deemed meaningful to answer the research questions was marked. In the second column, labelled *condensing*, marked text from the first column was printed out verbatim. In the third column, labelled *code*, the condensed text from the second column was given a label consisting of one or a couple of words that are close to the text (108). Thereafter, the codes were transferred and numbered into a coding scheme, and codes with something in common were divided into *categories and sub-categories*. The categories and sub-categories were constructed to differ from each other in a distinct way so that a code could only fit one category or sub-category. The analysis process was not static in one direction but moved back and forth between the whole transcribed text and the columns in the classification scheme, and were discussed by the authors until consensus was reached. For an example of the analysis process, see Figure 3.

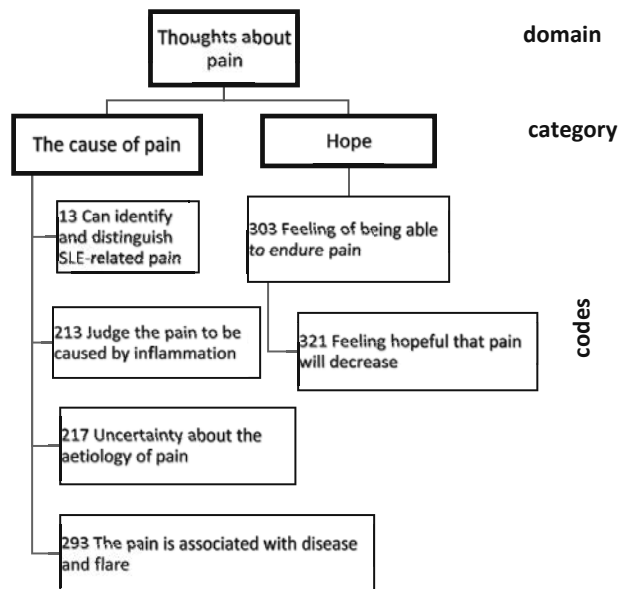


Figure 3. Example from the analysis process from codes to domain

8 ETHICAL CONSIDERATIONS

The studies were approved by the Stockholm Regional Ethical Review Board. All participants who were asked to participate in the studies, the inclusion, the 7-year follow-up and the interview study, received verbal information about the studies and procedures. It was stressed that participation was voluntary, and that the participant could discontinue the study at any time without giving any reason. Those who were interested in participating after receiving verbal information were provided with written information about the study, the name of the persons responsible for the study, and a telephone number for the Study Nurses in the event of questions or other issues. The participants were given the opportunity to read through the information in peace and quiet, generally in their home but in some cases at the hospital.

All participants provided written informed consent. The questionnaires were completed at the clinic to facilitate clarifying questions from the study participants during the procedure. This ensured there was little missing data. There was also time for questions and advice on health and the disease during the meetings with the nurses and the physicians. For any medical issues that emerged during the study visit, the controls were referred to appropriate healthcare providers. Feedback was also given on the results of the investigations. In the patient group, medical issues were managed at the clinic in agreement with the patient's regular treating physician and nurse. All participants were encouraged to contact the Study Nurses if they had any questions regarding participation and procedures in the study, even after completion.

The professionals in the study were aware of potential feelings of being forced to participate due to misguided loyalty or fear of negative consequences for their future care. Another identified negative risk was that the questions in the questionnaires could be considered as personally intrusive. To minimize this risk, the professionals emphasized continuously throughout the studies that participation was voluntary and that non-participation would not impact on future care and treatment.

9 RESULTS

9.1 STUDY I: PATIENT-REPORTED SLE-RELATED PAIN AND CHARACTERISTICS OF THE PATIENT POPULATION

The patients in the high-pain group reported significantly higher pain scores on VAS, median (IQR) 70 (62 to 79) compared to the patients in the low-pain group, 6.5 (1 to 17.5) ($p<0.001$) and accounted for 24% of the study population.

Disease duration (years) for the whole patient cohort was median (IQR) 9 (5 to 16) (Table 3). The high-pain group differed significantly from the low-pain group regarding shorter disease duration, higher disease activity measured by SLAM, SLEDAI and ESR, as well as higher global disease activity on VAS within SLAM (Table 6).

Table 6. Significant differences between the low-pain group and the high-pain group

	Low-pain group, n=64	High-pain group, n=20	p ^a
Disease duration, yrs ^b	10(5 to 17.5)	5.5(3 to 9.5)	0.008
Disease activity (SLAM) ^b	5.5(4 to 8)	10.5(8 to 14)	<0.001
Disease activity (SLEDAI) ^b	2(0 to 4)	4.5(2.5 to 9.5)	0.014
ESR, mm/h ^b	17(12 to 26)	27(13.5 to 43)	0.044
Disease activity measured by physicians (VAS mm/SLAM) ^b , n=27	7(3 to 11)	25.5(13 to 30)	0.029
Disease activity measured by patients (VAS mm/SLAM) ^b , n=81	13(8 to 23)	52.5(41 to 68.5)	<0.001

^aMann-Whitney U Test, ^bmedian with interquartile range (IQR), p value denotes statistical differences between the low-pain group and the high-pain group

There were no significant differences between the high-pain group and the low-pain group regarding the proportion of females and males, age, treatment with glucocorticoids and disease damage measured by SLICC (data not shown).

SLAM indicated clinically important disease activity only in the high-pain group whereas SLEDAI indicated mild disease activity in both the low- and the high-pain group. The Spearman's Rank Correlation Coefficient (r) between SLE-related pain and SLAM and SLEDAI, which included the whole patient cohort (n=84) was 0.44 and 0.35, respectively.

The physicians scored significantly lower global disease activity on VAS in SLAM, median (IQR) 12 (4 to 23) compared to the whole patient cohort 19 (10 to 50) (p=0.007).

9.1.1 Patient-reported pain characteristics and locations

Compared to the low-pain group, the high-pain group scored significantly higher pain intensity in the total, sensory, and in the affective pain intensity index of SF-MPQ. Moreover, the high-pain group indicated pain for more descriptive words (Table 7).

Table 7. Pain characteristics according to the short-form McGill Pain Questionnaire (SF-MPQ) in the low- and high-pain group

	Low-pain group, n=84	High-pain group, n=20	p ^a
SF-MPQ total intensity score for descriptive words ^b	2(0 to 5)	14.5(5.5 to 20.5)	<0.001
The SF-MPQ sensory index ^b	2(0 to 4)	13(7 to 17)	<0.001
The SF-MPQ affective index ^b	0(0 to 4)	8.5(4 to 10.5)	0.002
Descriptive words ^b	2(0 to 4)	8.5(4 to 10.5)	<0.001

^a Mann-Whitney U Test, ^bmedian with interquartile range (IQR), p value denotes statistical differences between the low-pain group and the high-pain group

The descriptive words most reported in the high-pain group as moderate were *stabbing* (n=6/30%), *burning* (n=9/45%) and *aching* (n=10/50%) and as severe *heavy* (n=5/25%), *exhausting* (n=5/25%) and *tender* (n=8/40%). In general, a larger proportion of the high-pain group, compared to the low-pain group, reported moderate and severe pain for each word in the SF-MPQ (Figure 4).

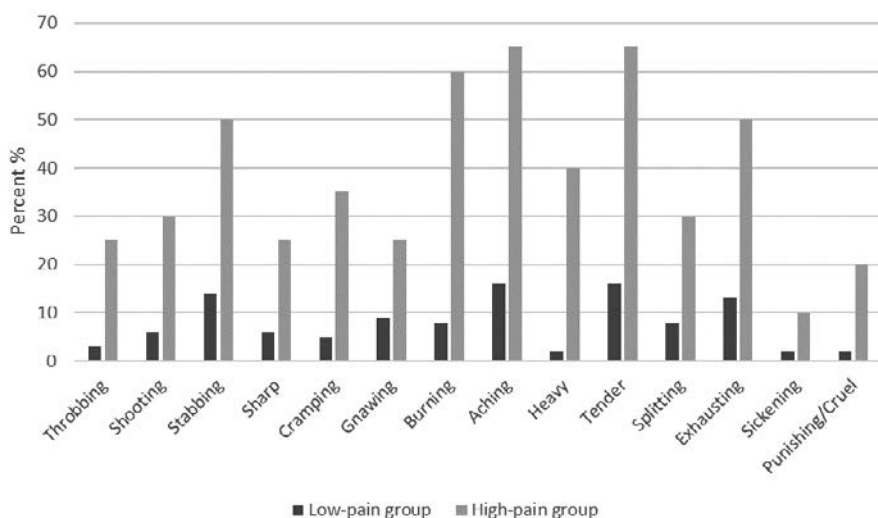


Figure 4. Descriptive words expressed as a percentage to signify moderate and severe pain in the low-pain group and the high-pain group

Most patients in the high-pain group (70%) denoted their present pain as *distressing*, and conversely, the low-pain group (55%) denoted *no pain* in the present pain index (PPI). There was a positive correlation between self-reported SLE-related pain on VAS and the number of descriptive words used; Spearman's Rank Correlation Coefficient (r) 0.78 when the whole patient cohort was included.

The most common pain location for the low- and high-pain group was the joints, even though only a minority exhibited objectively verified arthritis. Other locations for pain according to SLAM were the head, muscles and abdomen (Figure 5).

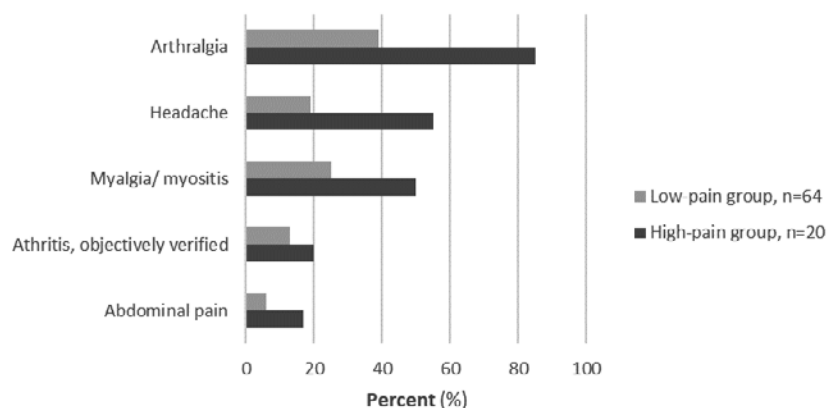


Figure 5. Distribution of pain location according to SLAM in the low- and high-pain groups

When looking at the whole patient cohort, patients with arthritis verified by the physician, had significantly shorter disease duration, median (IQR) 3 (1 to 11) years compared to those with no confirmed arthritis 9 (5 to 17.5) ($p=0.027$) years.

9.2 STUDY II: SELF-REPORTED OVERALL PAIN, HEALTH-RELATED QUALITY OF LIFE, FATIGUE, ANXIETY AND DEPRESSION

In Study II, the low- and the high-pain groups were compared to age- and gender-matched controls from the general population for pain, HRQoL, fatigue, anxiety and depression.

9.2.1 Self-reported overall pain

Overall pain on VAS was used for appropriate comparison between the patient cohort and the controls. In the patient cohort, overall pain exhibited the same pattern as for SLE-related pain with a significant difference between the low-pain group, median (IQR) 11 (2 to 22) and the high-pain group, 72 (64 to 80) ($p<0.001$). No significant difference was found between self-reported SLE-related pain and overall pain in the low-pain group or the high-pain group ($p=0.15$ and 0.06 respectively). The overall pain score for the controls, median (IQR) 5 (0 to 36), did not differ significantly from the low-pain group ($p=0.65$) but differed significantly from the high-pain group ($p<0.001$).

9.2.2 Self-reported health-related quality of life

The high-pain group reported a significantly lower score, meaning poorer HRQoL, in all dimensions of SF-36 compared to the low-pain group and the controls ($p<0.001$ to 0.005 and $p<0.001$, respectively) (Figure 6).

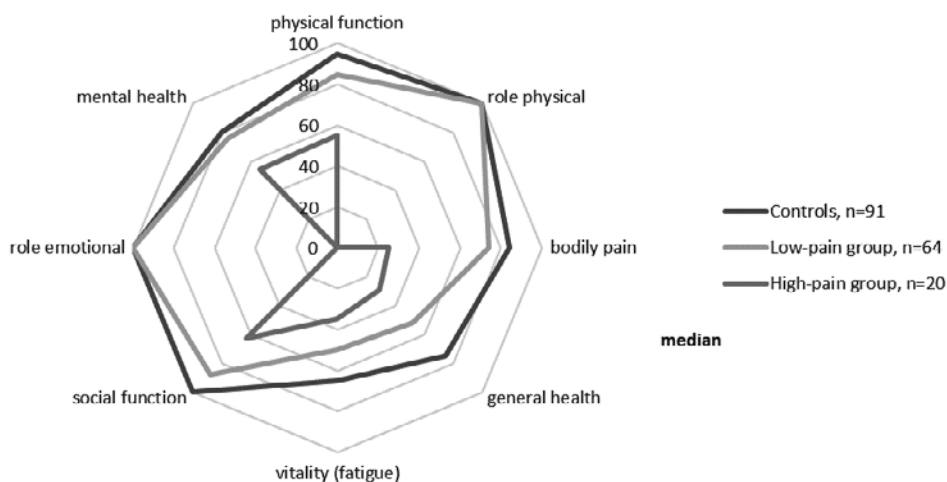


Figure 6. Scores as median by the controls, the low- and high-pain groups in all domains in SF-36

The low-pain group reported similar scores to the controls in half of the dimensions of SF-36. However, the scores by the low-pain group were significantly lower in the dimensions *physical function* ($p<0.001$), *general health* ($p<0.001$), *vitality* ($p=0.02$) and *social function* ($p=0.02$) compared to the controls.

Low-to-moderate correlations were found between scores in the dimensions of SF-36 (excluding bodily pain) and scores for overall pain in the patients; Spearman's Rank Correlation Coefficient (r) ranged from -0.29 to -0.54, and in the controls from -0.30 to -0.56. Further, the correlations between scores in the dimensions of SF-36 (excluding bodily pain) and SLE-related pain ranged from -0.43 to -0.58. The correlations between scores in the dimensions of SF-36 (including bodily pain) and SLAM ranged from -0.26 to -0.57 and SLEDAI from -0.17 to -0.38.

9.2.3 Self-reported fatigue

In the high-pain group, 50% of the patients scored fatigue every day compared with 33% in the low-pain group and 24% in the controls.

Fatigue, measured by the summary general fatigue index (GFI) in MAF, was significantly higher in the high-pain group, median (IQR) 36.5 (32.5 to 39.7), compared to the low-pain group, 23 (14.6 to 34.1) ($p<0.001$), and the controls 19.4 (11.6 to 29.1) ($p<0.001$). No significant difference was found between the low-pain group and the controls ($p=0.09$).

The Spearman's Rank Correlation Coefficient (r) between MAF/GFI and SLE-related pain, and MAF/GFI and overall pain in the patient cohort was 0.53 and 0.49, respectively, and in the controls the correlation between MAF/GFI and overall pain was 0.40.

The correlation (r) between MAF/GFI and the disease activity indices SLAM and SLEDAI was 0.48 and 0.29, respectively.

9.2.4 Self-reported anxiety and depression

The total anxiety index in HADS indicated symptoms of mild-to-moderate inconvenience for the patients in the high-pain group, median (IQR) 9 (6.5 to 11.5), whereas for the patients in the low-pain group and the controls, the total anxiety index indicated no symptoms of anxiety, median (IQR) 4 (3 to 8) and 4 (2 to 7), respectively.

The total depression index indicated no symptoms of depression in the high-pain group, median (IQR) 7.5 (5.5 to 9), in the low-pain group 3 (1 to 5) nor in the controls 2 (1 to 4). However, the high-pain group scored a significantly higher total index for anxiety and depression compared to the low-pain group ($p<0.001$) and the controls ($p<0.001$). No significant difference was found between the low-pain group and the controls regarding the total anxiety and depression index ($p=0.81$ and $p=0.19$, respectively).

The Spearman's Rank Correlation Coefficient (r) between SLE-related pain and the total anxiety index in the whole patient cohort was 0.43, and 0.52 between SLE-related pain and the total depression index.

9.3 STUDY III: SEVEN-YEAR FOLLOW-UP OF SELF-REPORTED PAIN, HRQOL, FATIGUE, ANXIETY AND DEPRESSION

9.3.1 Self-reported pain

When investigating the whole patient cohort ($n=64$) at the seven-year follow-up, there was no significant difference between inclusion, in this study named *year 0*, and the seven-year follow-up, named *year 7*, concerning intensity of self-reported overall pain and SLE-related pain during the previous week using VAS (Table 8a). When the patients were divided into groups by pain intensity which was scored at year 0, the patients in the high-pain group scored a lower level of overall pain and significantly lower SLE-related pain at year 7 compared to year 0 (Table 8a). However, the patients in the low-pain group ($n=50$) reported similar scores of overall pain and SLE-related pain at year 7 as they did at year 0 (Table 8a).

Table 8a. Overall pain and SLE-related pain at inclusion and seven-year follow-up in patients divided into groups by pain, and controls

	The whole patient cohort, n=64		p ^a	Low-pain group, n=50		p ^a	High-pain group, n=14		p ^a	Controls, n=68		p ^a
	Year 0	Year 7		Year 0	Year 7		Year 0	Year 7		Year 0	Year 7	
Overall pain, VAS, mm ^b	17 (3 to 45)	23 (6 to 45)	0.98	13 (3 to 23)	18 (4 to 35)	0.21	70 (49 to 79)	49 (14 to 70)	0.050	5 (0 to 29)	11 (2 to 30)	0.09
Change ^c in overall pain, VAS, mm ^b	na	0 (-12 to 15)	na	na	-1 (-12 to 6)	na	na	33 (-4 to 51)	na	na	-2 (-13 to 14)	na
SLE-related pain, VAS, mm ^b	11 (2 to 31)	11 (1 to 33)	0.92	7 (1 to 16)	8 (1 to 22)	0.19	69 (50 to 72)	43 (15 to 66)	0.035	na	na	na
Change ^c in SLE-related pain, VAS, mm ^b	na	1 (-7 to 7)	na	na	0 (-6 to 2)	na	na	32 (-13 to 48)	na	na	na	na
Chronic widespread pain/ACR90(42) ^d	na	20 (31%)	na	na	13 (26%)	na	na	7 (50%)	na	na	9 (13%)	na

^aWilcoxon matched pairs test, ^bmedian with interquartile range (IQR), ^cchange between year 0 and year 7, ^dnumbers (%), na=not applicable, p value denotes statistical differences between inclusion (year 0) and seven-year follow-up (year 7)

Table 8b. Self-reported pain, use of analgesics and disease activity in the patients with decreased and remaining pain at inclusion and seven-year follow-up

	Patients with decreased pain, n=7		p ^a	Patients with remaining pain, n=7		p ^a
	Year 0	Year 7		Year 0	Year 7	
Overall pain, VAS, mm ^b	67(51 to 71)	14(10 to 44)	0.031	78(46 to 96)	64(52 to 75)	0.92
Change ^c in overall pain, VAS, mm ^b	na	48(31 to 61)	na	na	-0.5(-18 to 35)	na
SLE-related pain, VAS, mm ^b	70(60 to 72)	15(2 to 37)	0.021	67(47 to 83)	66(55 to 73)	0.87
Change ^c in SLE-related pain, VAS, mm ^b	na	45(35 to 65)	na	na	-13(-20 to 28)	na
Problems SLE-related pain, VAS, mm ^b	na	15(3 to 29)	na	na	54(47 to 88)	na
Pain>3 months ^d	na	4(57)	na	na	7(100)	na
Chronic widespread pain/ACR90(42) ^d	na	0(0)	na	na	7(100)	na
Numbers of body regions with pain>3 months ^b	na	4(3 to 4)	na	na	11(9 to 15)	na
Use of analgesics regular ^d	na	1(14)	na	na	6(86)	na
Use of analgesics as needed ^d	na	4(57)	na	na	1(14)	na
SLAM ^{b,e}	12(7 to 19)	5(3 to 6)	0.018	9(5 to 14)	8(6 to 11)	0.40
Patients' reported global disease activity, VAS/SLAM, mm ^b	62(49 to 70)	6(3 to 34)	0.043	50(44 to 81)	50(49 to 73)	0.69
Physicians' reported global disease activity, VAS/SLAM, mm ^b	na	5(2 to 10)	na	na	15(9 to 17)	na
Difference between patients' and physicians' global disease activity, VAS/SLAM, mm ^b	na	4(1 to 24)	na	na	35(33 to 46)	na
SLEDAI ^{b,f}	7(3 to 16)	0(0 to 2)	0.046	2(0 to 4)	0(0 to 2)	0.36
SLICC ^b	1(0 to 4)	2(1 to 4)	0.11	0(0 to 2)	1(0 to 3)	0.043

^a Wilcoxon matched pairs test, ^b median with interquartile range (IQR), ^c change between year 0 and year 7, ^d numbers(%), ^e without lymphocytes, ^f without complement and ds-DNA, p value denotes differences between inclusion and seven-year follow-up

The change in SLE-related pain between year 0 and 7 was larger in the high-pain group median (IQR) 32 (-13 to 48) whereas it was 0 (-6 to 2) in the low-pain group.

Further analysis of self-reported SLE-related pain in the high-pain group at year 7 showed that half of the patients in this group (n=7) reported significantly lower level of SLE-related pain at year 7, and the other half of the high-pain group (n=7) reported an unchanged level of

SLE-related pain at year 7 compared to year 0 (Table 8b). Therefore, the high-pain group was further divided into two groups, patients with *decreased pain* and the patients with *remaining pain*, as illustrated in Figure 7.

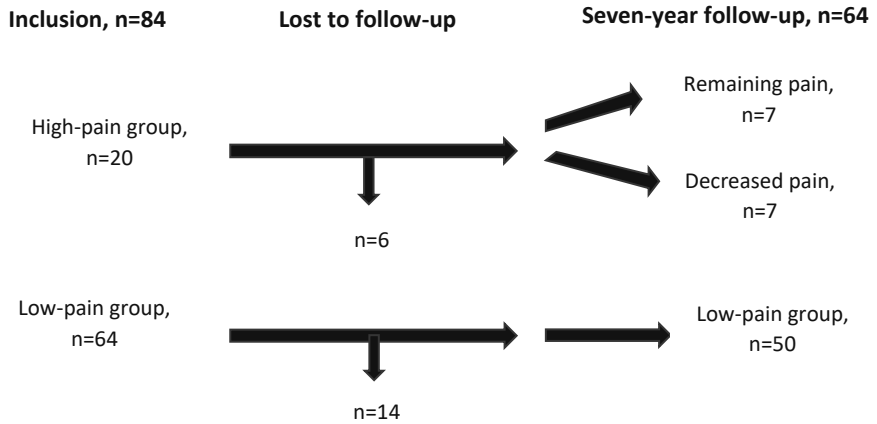


Figure 7. Division into groups by SLE-related pain intensity at inclusion and seven-year follow-up

All the patients with remaining pain reported pain lasting more than three months; the pain drawing indicated chronic widespread pain according to the definition by Wolf (42).

Comparison of pain and characteristics between the patients with decreased and remaining pain are presented in Table 8b.

No significant difference was found for overall pain between the controls and the low-pain group and those with decreased pain at year 7. However, when the controls were compared to the whole patient cohort ($n=64$) and to the patients with remaining pain, the controls reported significantly lower overall pain at year 7 ($p=0.032$ and $p<0.001$, respectively).

The score for the total pain intensity index of SF-MPQ and numbers of descriptive words used remained the same at year 7 as at year 0 for patients in the low-pain group and patients with remaining pain. However, patients with decreased pain reported a significantly lower total index at year 7, median (IQR) 2 (1 to 4) compared to 17 (5 to 22) at year 0 ($p=0.028$) and fewer descriptive words, 2 (1 to 3) at year 7, compared to 9 (7 to 11) at year 0.

9.3.2 Characteristics and medications

No significant difference in age or disease duration was found between the patient groups divided by pain; the low-pain group, the patients with decreased pain and remaining pain (data not shown).

All patients in the cohort had decreased medication in terms of DMARD and glucocorticoids at year 7. The largest dose reduction of glucocorticoids was found among the patients with decreased pain (milligram), median (IQR) 5 (0 to 12.5). All, except one, of the patients with remaining pain used analgesics regularly, $n=6$ (86%) compared to 12 (24%) of the patients in the low-pain-group and 1 (14%) of the patients with decreased pain.

9.3.3 Disease activity and damage

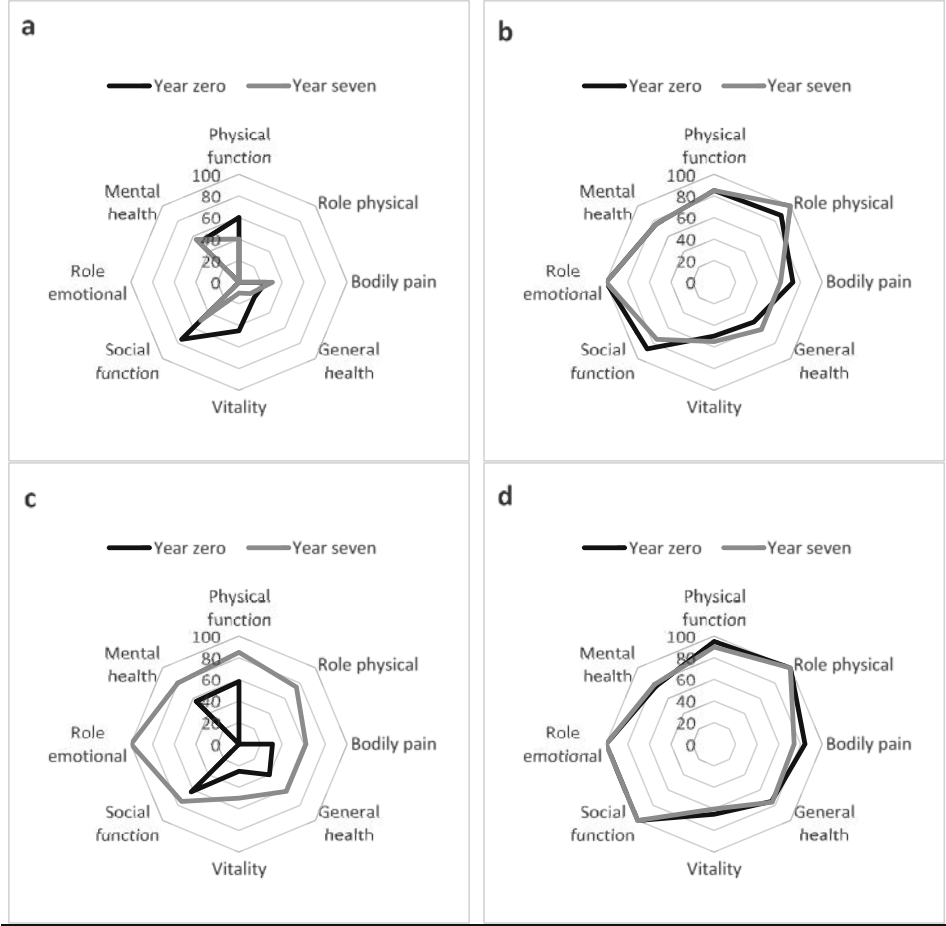
Disease activity according to the SLAM index was statistically unchanged between year 0 and year 7 for the patients with remaining pain, and significantly higher compared to the patients in the low-pain group and those with decreased pain ($p=0.006$ and $p=0.017$ respectively). Disease activity had decreased significantly according to the SLAM for the patients with decreased pain (Table 8b) and for the patients in the low-pain group at year 7, median (IQR) 4 (2 to 7) compared to year 0, 5 (4 to 8) ($p=0.007$). Conversely, there was no statistical difference between the patients in the different pain subgroups in regard to disease activity measured by the SLEDAI at year 7 (data not shown). The SLEDAI decreased significantly only in patients with decreased pain at year 7 (Table 8b). When comparing SLEDAI at year 0 for patients with decreased and remaining pain, the SLEDAI was higher in the patients with decreased pain at year 0, even though the difference was not statistically significant ($p=0.073$). Yet, there was no significant difference in the SLEDAI measured at year 0 for patients in the low-pain group and patients with remaining pain.

Global disease activity reported by the physicians on VAS in SLAM at year 7 was significantly lower compared to that reported by patients in the low-pain group, median (IQR) 5 (0 to 12), patients with decreased pain and patients with remaining pain (Table 8b) ($p<0.001$, $p=0.043$ and $p=0.028$ respectively). The largest difference was found between the physicians and patients with remaining pain (Table 8b).

Despite a higher damage index using SLICC in patients with decreased pain (Table 8b) at year 7, this was not significantly different from patients with low pain and patients with decreased pain.

9.3.4 Health-related quality of life

Except for a worsening of the dimension *vitality* of the SF-36, median change (IQR) -20 (-35 to -15) at year 7, there was no other significant difference in the dimensions of the SF-36 between year 0 and year 7 for patients with remaining pain (Figure 8a). Patients in the low-pain group scored similar levels at year 7 as at year 0 in all dimensions of the SF-36 except for a reduction in the dimensions *physical function*, median change (IQR) 0 (-10 to -5), and *bodily pain*, 0 (-21 to 1) (Figure 8b). Conversely, patients with decreased pain scored improvement in all dimensions of the SF-36 (Figure 8c).



Figures 8 a-d. Health-related quality of life (SF-36) (range 0-100), presented as median, for patients with SLE, grouped by SLE-related pain and controls at year 0 and year 7. **a** patients with remaining pain, **b** patients in the low-pain group, **c** patients with decreased pain, **d** controls

Except for the dimension *mental health* of the SF-36, patients with remaining pain scored a lower HRQoL at year 7 in all dimensions of the SF-36 than patients in the low-pain group, patients with decreased pain and the controls ($p < 0.001$ to 0.012). However, there was no difference at year 7 in any dimension of the SF-36 between patients in the low-pain group and patients with decreased pain.

No significant difference was found between year 0 and year 7 in any of the dimensions of the SF-36 for the controls (Figure 8d). Nor was there any difference between controls and patients with decreased pain in any dimension of the SF-36. However, the controls scored significantly better for HRQoL compared to patients in the low-pain group in the dimensions *physical function* ($p = 0.016$), *general health* ($p = 0.007$), *social function* ($p = 0.023$) and scored close to significant in *bodily pain* ($p = 0.053$).

9.3.5 Self-reported fatigue

The score for GFI/MAF was unchanged between year 0 and year 7 in patients with remaining pain (Figure 9) and these patients also scored significantly higher GFI at year 7 than patients in the low-pain group ($p = 0.017$), patients with decreased pain ($p = 0.017$) and the controls ($p = 0.001$). In contrast, patients with decreased pain scored significantly lower GFI at year 7 compared to year 0, whereas patients in the low-pain group and the controls scored similar levels of GFI at year 0 and year 7 (Figure 9). No significant difference in GFI at year 7 was detected between the patients in the low-pain group, the patients with decreased pain, or the controls.

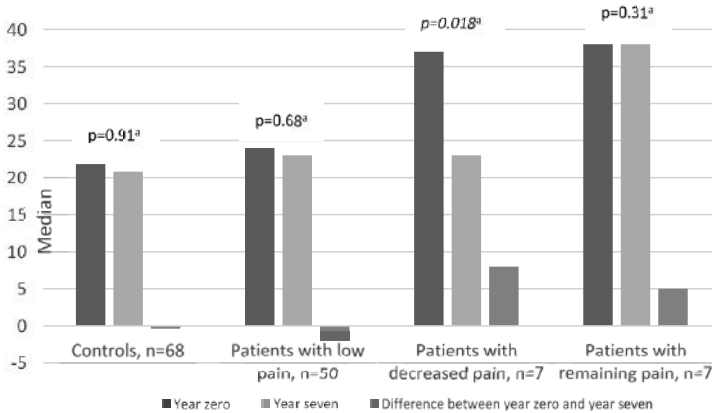
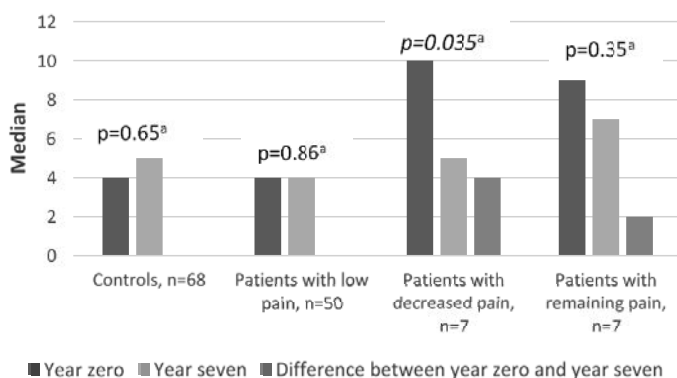
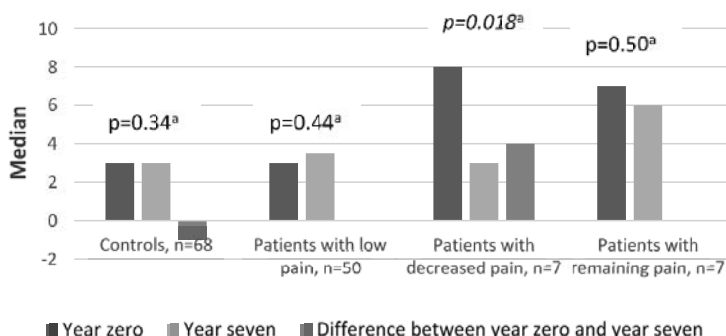


Figure 9. General fatigue index (GFI/MAF) (range 1-50) for patients with SLE as grouped by SLE-related pain and controls at year 0 and year 7,

^a Wilcoxon Matched Pairs Test

9.3.6 Self-reported anxiety and depression

No symptoms of anxiety or depression were found in the total indices of HADS at year 7 in any patient in the pain subgroups nor in the controls. Patients with decreased pain scored a significantly lower total index for both anxiety and depression. Moreover, there was no significant difference in scores for the anxiety total index at year 7 between the patient groups: low-pain group, patients with decreased pain, and patients with remaining pain, nor for the controls (Figure 10a). However, patients with remaining pain scored a significantly higher total index for depression than patients in the low-pain group, patients with decreased pain and the controls (Figure 10b).

a**b**

Figures 10 a+b. HADS, total index for anxiety and depression (range 1-21) for patients with SLE as grouped by SLE-related pain and controls at year 0 and year 7, **a** total index for anxiety, **b** total index for depression, ^a Wilcoxon Matched Pairs Test

9.4 STUDY IV: INTERVIEWS WITH PATIENTS WITH SLE-RELATED PAIN

The transcribed text from 20 interviews produced 296 codes which created 39 categories and 34 subcategories. Saturation, the point at which no new codes were obtained, was reached after the 15th interview. The categories and subcategories were further divided into seven domains which were defined by the questions in the interview guide and by the narratives from the informants (Figure 11).

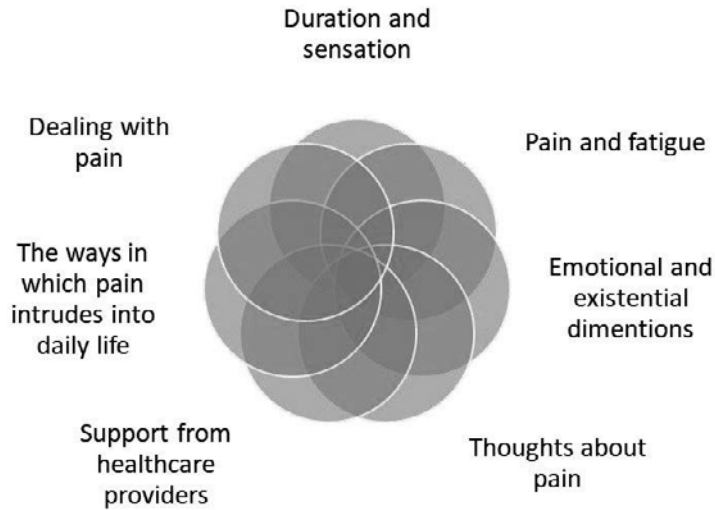


Figure 11. The seven domains that emerged from the interviews

9.4.1 Duration and sensation

The pain was portrayed by the informants as long-standing and always present, as well as migrating between different body areas including throughout the whole body. The pain intensity and duration in different body areas could vary over time and during the day. Typically, the informants related that the nature of the pain was unpredictable, hard to describe and similar to the pain with flu or after tough exercise. Mainly, the pain was located in the musculoskeletal system, but the informants also commented on headache, pain in the abdomen and the lungs, pain from wounds, blisters and rashes as well as pain related to Raynaud's phenomenon. The intensity of the pain could be intrusive and require all their concentration; sometimes, however, it was possible to be distracted.

Several factors could trigger or exacerbate the pain such as stress or other emotions. Other common triggers were physical activity and environmental factors such as cold and changing weather. Getting relief from pain after making extensive lifestyle changes was also described:

".... I made a sound a sensible decision and closed down my business and took a job ... so it's probably the fact that life is less hectic that's made the pain disappear (#5)

9.4.2 Pain and fatigue

Pain and fatigue were closely linked and reinforced each other. Almost always, pain was followed by a loss of energy and physical weakness, causing physical as well as mental

fatigue which reduced the ability to carry out daily activities. Because of this interdependent relationship between pain and fatigue, the informants' ability to deal with pain was dependent on the degree of fatigue.

9.4.3 Emotional and existential dimensions

Several emotions were connected to pain including anger, despair, sadness, fear, hopelessness and self-pity. Frustration and irritation were expressed at the pain-associated limitations in daily life. The informants reflected on how their life with a chronic disease, such as SLE and pain, had turned out and asked themselves: *why me?* They also identified future dreams and plans which could not be realised because of the pain and their future sometimes felt uncertain:

"... I wasn't able to work, I can't, I can't stand up for very long, so all my dreams have come to nothing ..." (#6)

However, the informants felt, at least in part, that SLE and related pain was something that was now incorporated into their lives and considered illness like a cold or flu and something affecting them over and above their everyday life with SLE.

9.4.4 Thoughts about pain

The informants' thoughts about pain included the cause of pain and hope of improvement. They associated their pain to flares of an inflammatory condition (SLE) and they considered themselves able to distinguish SLE-related pain from other sources of pain. Thus, they might still be uncertain about the actual cause of the pain. The hope of improvement included the ability to endure pain.

9.4.5 The ways in which pain intrudes into daily life

The impact of pain in daily life could be divided into five dimensions (Figure 12).

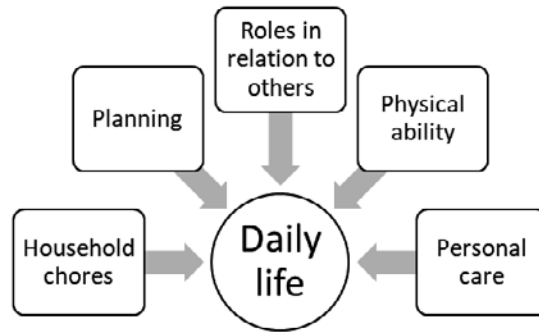


Figure 12. Five dimensions in daily life affected by pain

Limitations of the **physical ability** included difficulties with mobility, reduced strength and impaired balance. **Personal care** was also highlighted by the informants such as difficulties with dressing, putting on and off shoes and taking medicine out of a box. Difficulties with different **household chores** included cooking, cleaning and heavy lifting. Difficulties with **planning** were mainly related to the unpredictable course of the pain. The pain could impact the informants' ability to carry out different **roles in relation to others** such as family, partner, children, friends and co-workers. The pain-related limitations created dependence on others which in turn created guilt and the feeling of being a burden to others:

"... if I hadn't been in this situation, my relationships and finances might have been completely different..." (#8)

However, family members were considered to give valuable help and support.

9.4.6 Dealing with pain

The informants used several strategies to reduce pain and its impact on daily life. The strategies could be divided into two main areas which could be used alternatively and/or simultaneously:

Inner resources included; *acceptance, acquired knowledge/experience, adaption, conscious choices, inherent characteristics, repression and willpower*:

"... I don't think they notice so much at work, because you try ... I really try to keep it together" (#15)

Practical actions included; *aids/devices, cures/practical interventions, medication, and physical activity*.

These strategies resulted in varying degrees of pain alleviation and benefit, but rarely complete pain relief. The informants could also be unsure as to whether the strategies were efficient.

Despite the negative impact of pain, the informants found that pain could at least in some way contribute to self-development, such as inner strength, and to appreciating other aspects of their life. They also thought that their experience of pain increased their ability to understand the difficulties of others.

9.4.7 Support from healthcare providers

The invisibility of pain was identified by the informants as a reason for communication barriers between the patients and healthcare providers. Lack of confirmation of the pain by healthcare providers created feelings of being neglected, not being taken seriously or not being seen as credible. Conversely, being treated well and acknowledged by healthcare providers created security, confidence and gave hope. Therefore, the informants' earlier experiences of meeting healthcare providers were the starting point when they expressed suggestions for interventions from healthcare providers that were intended to support the informants' ability to deal with pain. The suggestions included the following topics: *be treated well and acknowledged, good accessibility to different professions, not being a messenger in their own care, alternative ways of maintaining contact, individually-tailored advice and information, interventions and support irrespective of economic circumstances, rehabilitation in warm climate, development of care and better treatment including medication:*

"... then they look in the records and say ... oh yes, you've had a problem with SLE ... it might be the SLE ... go and see the rheumatologist ... and so I go to the rheumatologist ... why have you come here with that problem, you should go to the healthcare centre ... and so you're bounced backwards and forwards and then you end up in emergency because someone thinks that's best and then they say ...what are you doing here ... and it's always us patients who get the blame if it isn't right ... so then you apologise and in the end no-one ... you don't go unless you really have to ... and then you just get ... why didn't you come earlier?" (#8)

10 DISCUSSION

10.1 SELF-REPORTED PAIN, HRQOL, FATIGUE, ANXIETY AND DEPRESSION

Overall, the studies in this thesis showed that most patients with SLE reported low intensity of disease-related pain. Moreover, the pain tended to decrease in intensity over time and with the course of the disease. Despite these gratifying results, a substantial proportion of the current cohort (24%) reported high intensity of disease-related pain (VAS \geq 40 mm) at inclusion (year 0) and, for some of these patients, the pain remained from year 0 to year 7. Despite the fact that high pain intensity occurred in a minority of the present cohort, the results clearly demonstrate a high symptom burden with impaired HRQoL, more fatigue, and more symptoms of anxiety and depression in these patients. Therefore, the patients with high pain intensity are in need of special attention from healthcare providers.

Earlier studies have reported poorer HRQoL in general among patients with SLE compared to the general population (17, 18, 66, 112). However, in this thesis, patients in the low-pain group did not differ from the controls in any significant way in regard to HRQoL except for worse scores in the dimensions *physical function*, *general health* and *social function* of the SF-36 at both year 0 and 7. Thus, the results concerning HRQoL emphasize the importance of identifying subgroups among patients with SLE to enable identification of important differences. Pain in SLE appears to be an important symptom which, if treated, will improve HRQoL because decreased pain has been shown to be associated with improved HRQoL (69), and freedom from pain is identified as a predictor for better HRQoL (67). Gallop et al (23) illustrated the great impact of subjective symptoms like pain on HRQoL in a conceptual model which emphasized the benefits for health if subjective symptoms are treated.

As expected, in this thesis the score for fatigue was higher in patients with higher levels of pain thereby confirming previous studies that had suggested a close relationship between pain and fatigue (28, 30, 71). More surprisingly, the results revealed that the patients in the low-pain group did not differ significantly from the controls in regard to fatigue.

As there were no significant signs of anxiety or depression in any patients grouped by pain or in the controls at year 7 (113), anxiety and depression appear to be the symptoms least affected by pain in this cohort. Further, patients with remaining high pain intensity at year 7 did not differ significantly from patients in the low-pain group, patients with decreased pain, and the controls in regard to the anxiety total index in HADS and the dimension *mental health* in SF-36. Thus, the results for mental health from study III tended to contradict a

previous study by Bachen et al (19) who found poorer mental health among women with SLE compared to the general population.

Results from the interview study (Waldheim et al 2018, manuscript), in which all the informants had reported high intensity of SLE-related pain at least at some point, confirmed the results from the questionnaires and expanded the knowledge on the impact of pain in SLE. These deeper insights on the impact of pain on health and daily life were not possible to obtain with questionnaires alone. However, the questionnaires appeared to be valuable for screening health status and symptoms.

The results from the interviews highlighted that SLE-related pain is one of the hardest-to-live-with symptoms, as reported in a recent study by Morgan et al (114). Moreover, the results from study IV were mainly consistent with the results from a review by Sutanto et al (115) which included 46 qualitative studies and showed that the informants with SLE described disease-related pain as unpredictable, disabling and interfering with daily activities such as personal care, work and exercise. Further, similarly to the informants in study IV, the informants in the review by Sutanto et al (115) depicted that stress and the weather could exacerbate pain, and some related that there was a lack of understanding from their surroundings and healthcare providers for invisible symptoms such as pain.

In summary, the repeated, similar results from studies in different countries, mainly in western countries, clearly demonstrate that pain is associated with a high symptom burden and subsequent negative impact on health and daily life. Targeted interventions from healthcare providers are therefore needed to support the patients in alleviating and dealing with pain. Further, the results from this and previous studies highlight the importance of measuring health status and subjective symptoms in clinical settings when exploring subjective outcomes of care and medical treatment.

10.2 SELF-REPORTED PAIN AND DISEASE DURATION

In study I, disease duration was significantly shorter in the high-pain group compared to the low-pain group. This result indicates that pain in SLE tends to be less common and have less intensity later in the course of the disease. This has also been reported in the study by Leuchten et al (47). Furthermore, It has been shown that the inflammatory activity decreases with time over the natural course of the disease (13); moreover, treatment duration increases, resulting in better control of the inflammation and associated symptoms. The patients may also acquire skills to manage pain. Accordingly, pain intensity decreased in the high-pain group at year 7, but only among the half of the patients. Therefore, the results from year 0 and

year 7 suggest the possibility of transition from pain induced by inflammation in the early course of SLE to pain induced by other mechanisms in the pain processing pathways (34, 43, 45, 46). This hypothesis is supported by the reported higher prevalence of fibromyalgia syndrome in patients with SLE (17 to 40%) compared to the general population (3-5%) as well as proposals for common mechanisms in SLE and fibromyalgia syndrome (116). However, the results from this thesis did not provide answers as to the cause of the pain, and neither was this the aim of the studies. Further studies and larger cohorts are required to investigate different mechanisms behind prolonged pain in patients with SLE and other rheumatic diseases.

10.3 SELF-REPORTED PAIN AND DISEASE ACTIVITY

At year 0, there was a significant difference in disease activity between the patients in the low- and high-pain group, where both SLAM and SLEDAI were significantly higher in the high-pain group. This can be explained by inadequately controlled inflammatory activity in patients with shorter disease duration, such as in the high-pain group. However, in the patients with remaining pain, SLAM was unchanged after seven years and was significantly higher compared to patients in the low-pain group and patients with decreased pain. However, there was no significant difference in SLEDAI between the patients grouped by pain at year 7, which suggests that pain rather than inflammatory activity impact the SLAM. For example, fibromyalgia syndrome is known to interfere with ratings of disease activity and may lead to a higher disease activity index (117). Further, SLAM includes more subjective variables than SLEDAI (95), and thereby subjective symptoms like pain and fatigue have a larger impact on the SLAM index.

The discrepancies in reported global disease activity on VAS/SLAM between the patients and the physicians, as well as disparity between SLAM and SLEDAI, indicate a risk of communication barriers. As shown before, patients with SLE report their disease activity based on more subjective experiences including the impact of the disease on life as a whole (118). In contrast, healthcare providers base their assessment on more commonly regarded objective measures such as laboratory findings and physical examinations (18, 119, 120). It is also known that a higher degree of pain correlates to greater discordance between patients and physicians (121).

10.4 SELF-REPORTED PAIN AND UNMET NEEDS

In the interview study (Waldheim et al 2018, manuscript), the informants expressed feelings of not being taken seriously when they talked about their pain with healthcare providers. The

informants thought this lack of acknowledgement was due to the invisible nature of pain. They also perceived that their pain was trivialized and that they were used as messengers in their own care. These dissatisfactions over unmet needs were also found in a review by Serrano-Aguilar et al (8), where pain was one of the most frequently reported health problems in patients with SLE. In that review, the patients thought the lack of attention to pain by healthcare providers was due to the non-life-threatening nature of the pain. The authors also found there was dissatisfaction with the poor coordination between different healthcare providers. Even though pain was not the focus in the study by Hale et al (122), the informants with SLE expressed dissatisfaction with not being listened to when relating their problems, as well as dissatisfaction with a lack of coordination between different healthcare providers. In a recent study by Golder et al (123), the authors suggest that the different priorities of concerns create a barrier in communication between patients and healthcare providers.

10.5 INTERVENTIONS TO REDUCE PAIN

In study IV, the informants used many strategies to deal with pain, both inner resources and practical actions as well as combinations of these. Despite these strategies, adaption to their situation and the extensive energy used, the informants did not achieve complete relief from pain. However, they could identify areas which they thought could be beneficial when dealing with pain, and which should be taken into account when developing and implementing new interventions aimed at alleviating pain.

Based on previous studies, interventions for conditions with longstanding pain should be multidisciplinary (40, 51, 52). As confirmed in the study by Serrano-Aguilar et al (8), involving patients in the development of clinical guidelines in which their needs are addressed is one way to approach person-centred care and to implement individual targeted interventions.

The informants in study IV commented on physical activity as beneficial to increase their wellbeing when pain is a major symptom. However, physical activity could also trigger pain and thus it was hard for the informants to reach the beneficial level of physical activity. In a previous study by Arvidsson et al (67), regular low intensity exercise promoted HRQoL in patients with a variety of rheumatic diseases. In contrast, a previous study by Boström et al (124) investigating high intensity exercise in patients with SLE, did not show any significant improvement in HRQoL. On the other hand, it was found that high intensity exercise did not negatively impact the disease in patients with mild to moderate SLE disease activity.

Another study by Arvidsson et al. (52), which looked at a problem-based learning (PBL) intervention, showed improved empowerment in patients with various rheumatic diseases and chronic musculoskeletal pain. Greco et al (51) found a positive effect of acupuncture in a randomized pilot study and Yuen et al (125) found beneficial effects on pain, fatigue, anxiety and depression using an interactive video system.

Despite the fact that there are few intervention studies aimed to reduce pain and improve health in patients with SLE, some report positive results and thereby give hope for future research and development of individual targeted interventions.

11 METHODOLOGICAL CONSIDERATIONS

The post hoc power analysis which was performed at year 0 (126) showed low power when comparing patients in the low-pain group to the controls. However, this low power strengthens the results in this thesis by revealing that patients in the low-pain group were so similar to the controls that a difference is hard to detect. The post hoc power analysis showed that a large cohort was needed to detect a difference between the low-pain group and the controls; this was not possible to include in the studies for this thesis. The relatively small cohort size and the cross-sectional design in studies I-III could limit generalization of the results. However, because most patients with SLE in Sweden should be affiliated with a rheumatologist (127-129), the cohort was considered to be representative for the disease. The low proportion of men to women did not allow comparison between genders, especially when divided into smaller groups for reported pain at year 7. Both the patients and the sex- and age-matched controls were recruited from the same greater urban area which made the comparisons between patients and controls reliable.

For ethical reasons, no data were collected from patients who participated at year 0 but who declined to participate at year 7. This prevented comparison between those who participated and those who did not. Thus, it cannot be excluded that this thesis would have produced different results if data for those who declined to participate had been included.

Notwithstanding, at year 7, age and disease duration were compared for those who participated and those who did not (from the original cohort), because this did not require collection of new data. As far as we know, few studies have investigated self-reported SLE-related pain, HRQoL and other associated symptoms in the same cohort after seven years, and it cannot be expected that all participants from inclusion are willing to participate again. The choice of timepoint for follow-up, seven years, was due to external circumstances. However, considering the chronic course of SLE, all follow-up is valuable for understanding the impact of the disease.

All of the self-assessment questionnaires used in this thesis are generic and not all have been tested for validity and reliability in the context of patients with SLE. However, the questionnaires are frequently used in research on patients with SLE and in different rheumatology settings, and thereby allow for comparison between different studies and cohorts of patients with SLE and other rheumatological diseases. Further, the generic nature of the questionnaires allows for comparison with patients with diseases other than those within rheumatology (20, 28, 95, 114). However, the SF-36 has previously been tested for reliability and validity in patients with SLE (65, 92-94) and in Swedish populations (90, 91).

Further, SLE is considered a relatively uncommon disease and testing reliability and validity of questionnaires for patients with SLE fell outside the scope of our present studies.

There are both advantages and disadvantages of using VAS in measuring pain intensity. Among the advantages is it is simple to implement, which is the reason it is frequently used in clinical practice; VAS was therefore familiar to most of the study participants in the studies presented in this thesis. The division of the patients into subgroups using scored pain intensity on VAS was considered useful to demonstrate the heterogeneous nature of SLE. The differences in a cohort population with SLE would not otherwise be detected nor would the similarities to the controls from the general population. Cut-off values have been used earlier in a study by Burgos et al (28), in which the median of VAS pain was used as a cut-off value. They found, as we did in our studies, that a higher pain score corresponded with a higher fatigue score. However, the cut-off value creates a border for values close to the cut-off value. For example, scoring 38 or 43 mm on VAS may not have any clinical implication. The cut-off value should therefore be considered as a research tool for highlighting a topic.

One disadvantage with VAS is its one-dimensional nature, and the challenge mainly consists of transforming a subjective experience into one single measurement. To meet this challenge, SF-MPQ was used to provide additional and more detailed information on pain. The descriptive words used by the patients in the SF-MPQ displayed a picture of the patients' experiences which were later expanded through the narratives in study IV. In addition, SF-MPQ is preferred for use with patients with longstanding pain (84). However, a score on VAS was judged to be more convenient when dividing the patients into two groups at year 0 for further comparisons. Moreover, the additional patient-reported measurements regarding HRQoL, fatigue, anxiety and depression contributed to the multidimensional perspective of pain.

The SF-36 was chosen to measure health, and since SF-36 has been developed to measure HRQoL, uncertainty could arise concerning the concepts used in this thesis. For clarification, SF-36 was considered appropriate to use since the attributes in the definition of health by the WHO, physical, mental and social well-being, are represented in the measurement.

The questionnaires were completed at the clinic in conjunction with the visit in the SLEVIC study, both at year 0 and year 7. This procedure enabled the study participants to ask questions if needed and resulted in few missing data. Despite this, some data were missing. Issues regarding missing data of descriptive words in SF-MPQ, were resolved through dialogue with Professor Ronald Melzack who constructed the measurement (86). The advice

from Professor Melzack was to first determine whether the missing values were meant to be zero (no pain) based on the patient's other replies. If it was suspected that the reply was not zero (no pain), we took the average of the other descriptors, and added this to the incomplete subtotal.

In a recent study, a moderate-to-good correlation was found between SLAM/SLAM-no lab and a Swedish version of the self-reported Systemic Lupus Activity Questionnaire (SLAQ) (130). The results from that study may indicate that the discrepancy found in this thesis between the patients' and the physicians' assessment of disease activity, at least partly, depends on which method or assessments are used. In addition, the physicians' assessment of disease activity on VAS has earlier been criticized as being too blunt (131).

Disease activity, at year 0, measured by SLAM and SLEDAI included laboratory parameters lymphocytes, ds-DNA and complements. However, at year 7, these laboratory parameters were not included. Therefore, it cannot be excluded that comparison of disease activity between year 0 and year 7 would have yielded different results if the laboratory parameters had been included for both years. To address this, SLAM and SLEDAI at year 0 were also converted to SLAM without lymphocytes (SLAM-no lab) and SLEDAI without ds-DNA and complements (SLEDAI-no lab) for appropriate comparison.

To increase the reliability of the results in the interview study, the context for the study was described, and the use of a coding scheme made it possible to follow the different steps in the analysis process. Discussions were held between the authors until agreement was reached to overcome the subjectivity of the interpretation in the different stages of the analysis process. Further, the quotes illustrated and created links between the text data and the resulting categories and subcategories (108, 111). There are advantages and disadvantages of individual interviews compared to focus group interviews. One advantage is privacy where the informants may express feelings and opinions without being scrutinized or inhibited by others. A disadvantage may be a feeling of being overlooked by the interviewer and not being able to share inspiration and new perspectives from other members of a group.

12 CLINICAL IMPLICATIONS

The results from the studies in this thesis clearly point out the heterogenous nature of SLE and the importance of assessing patient-reported outcomes to trace patients with a high symptom burden like pain, regardless of disease activity. Further, the patient subgroups in which pain is present to a varying extent claim that individual adapted interventions and support will help patients to better deal with pain and will improve health. Differences in the assessment of disease activity by patients and healthcare providers indicated different perspectives and focus. This should be taken into account in communication between patients and healthcare providers to avoid patients feeling that they are not being taken seriously. The healthcare providers should facilitate the patients' understanding of the various causes which could underlie pain in SLE, and thereby enable them to better deal with pain. Further, acknowledging the patient's symptoms and experiences is an obvious and fundamental obligation for healthcare providers which will avoid adding to an already existing symptom burden.

Measuring pain as well as other patient-reported outcomes in clinical practice can be used as a basis for discussion between the patient and the healthcare provider, and enable self-reported outcomes to be put in context. In cases of high pain intensity and low disease activity (as judged by the healthcare provider), it is crucial to delineate the cause of pain. Even if the cause is not fully understood, it is important to provide the patient with available facts and alternative explanations. This will help the patient who feels uncertain and misunderstood and who is not adhering to medication. For example, when there are no objective signs of disease activity, but long-standing generalized pain like central sensitization is suspected, it is important to inform and involve the patient, something which in itself is considered to be an intervention (43).

Organizational and structural barriers between the various disciplines in the healthcare system may also prevent patients with SLE and pain from receiving appropriate care. Even though there are many positive consequences when patients participate in their own care, it cannot be assumed that the patients themselves will act as messengers between the various disciplines and healthcare providers. Therefore, networks should be developed between the disciplines and professions to create multidisciplinary care based on current knowledge and evidence.

13 SUMMARY AND CONCLUSIONS

As far as we know, few studies have been conducted in which SLE-related pain constitutes the main focus, and in which HRQoL, fatigue, anxiety and depression have been investigated based on the degree of pain. The approach using identification of patients into subgroups by pain intensity score clearly demonstrates that patients with SLE are a heterogeneous group in regard to pain. Earlier studies have shown that patients with SLE, in general, report more pain, a poorer HRQoL, a higher level of fatigue, and more anxiety and depression compared to the general population. However, the results from this thesis add to the current base of knowledge by showing that subgroups of patients with SLE have different symptom burdens, and that disease-related pain appears to be an important promotor of poorer HRQoL and exacerbation of fatigue. The patients with a high degree of pain also expressed a high impact of pain on daily life. They depicted difficulties with performance of practical activities, maintenance of their different roles and relationships with family and others. In contrast, patients with a low degree of pain did not deviate from the general population in any significant way. Anxiety and depression seemed to be least affected by pain. Furthermore, the results from this thesis showed that decreased pain was followed by improvement in HRQoL and fatigue as well as less anxiety and depression. The results also revealed a discrepancy in estimated disease activity by the patients and the physicians. The largest discrepancy was found in the patients with high pain intensity which could potentially create communication barriers. In addition, the patients with a high level of disease-related pain felt that, because of the invisible nature of the pain, the healthcare providers were sceptical to their complaints. They also perceived themselves to be messengers in their own care.

These results highlight the great importance of paying attention to pain in patients with SLE in clinical practice, and to develop interventions aimed to alleviate pain and to support the patients in dealing with pain.

14 SUGGESTIONS FOR FUTURE RESEARCH

Despite advances in neuroscience and new insights and knowledge on central and peripheral pain processing, many areas remain unclear on persistent pain in SLE and other rheumatology diseases, not least how to treat them. Taking into account the high symptom burden and poorer health associated with pain in SLE as well as the chronic course of the disease, future intervention studies aimed to support patients with SLE to better deal with pain appear to be of great importance. Proposals for future research areas include healthcare providers as well as patients, and when appropriate, significant others:

- multidisciplinary interventions and educational programmes for patients with SLE to help the patients better deal with pain
- rehabilitation interventions to diminish the impact of pain on working life and subsequent economic consequences
- interventions to increase and strengthen patients' involvement in healthcare
- implementation of tools to evaluate patients' satisfaction with healthcare
- adaption and implementation of appropriate disease activity indices for SLE in order to improve the communication on disease activity between patients and healthcare providers
- educational interventions for healthcare providers about pain and related symptoms
- educational interventions for healthcare providers about ethical approaches and response to the needs of patients with pain.

Further research close to clinical settings emerge as crucial. Patients with SLE and pain should be invited to participate in clinical research as a part of their treatment. Hopefully this would signal that pain is a symptom that deserves attention in the healthcare system and would give hope for the future.

15 SVENSK SAMMANFATTNING

Bakgrund

Att insjukna i en sjukdom med ett kroniskt förlopp innebär för de flesta människor utmaningar att förhålla sig till. Systemisk lupus erythematosus (SLE) är en autoimmun reumatologisk sjukdom som anses vara kronisk, dvs. en sjukdom där det i nuläget inte finns någon botande behandling men där det finns möjlighet att med läkemedel minska sjukdomsaktiviteten och därmed symptomen. Sjukdomen förlöper vanligen i oförutsedda skov, där perioder av låg sjukdomsaktivitet avlöses av perioder med högre sjukdomsaktivitet. I princip kan alla organ i kroppen drabbas och ge upphov till organspecifika symptom men det förekommer också allmänna symptom som feber, sjukdomskänsla och trötthet. Sjukdomens allvarlighetsgrad varierar stort mellan olika individer, från att vara en mycket mild till att vara en allvarlig sjukdom. Generellt anses patienter med SLE uppleva mer smärta, sämre hälsorelaterad livskvalitet, mer trötthet, oro och nedstämdhet jämfört med befolkningen i övrigt. Olika symptom kan också påverka varandra, till exempel kan smärta och trötthet förstärka varandra. De beskrivna symptomen och det kroniska förloppet på sjukdomen innebär att patienter med SLE löper risk för försämrad hälsa och begränsningar i vardagslivet.

I denna avhandling fokuseras huvudsakligen på SLE-relaterad smärta och hur smärtan påverkar hälsan. Begreppet hälsa definieras i enlighet med WHO:s definition att hälsa är ett tillstånd av fullständigt fysiskt, mentalt och socialt välbefinnande, inte endast frånvaro av sjukdom och funktionsnedsättning...Hälsa i förhållande till upplevd livskvalitet benämns här som hälsorelaterad livskvalitet.

Trots att framsteg har gjorts inom det medicinska omhändertagandet av patienter med SLE, så visar studier att patienter med SLE fortsätter att rapportera smärta och sämre hälsorelaterad livskvalitet än befolkningen i övrigt. Därtill finns det studier som visar att patienter med SLE upplever att vårdgivare inte uppmärksammar smärta vid SLE i tillräckligt hög grad. Sammantaget gör detta att mer detaljerad kunskap behövs om i vilken omfattning patienter med SLE rapporterar smärta, dess karaktär och hur smärtan förhåller sig till hälso-relaterad livskvalitet och andra subjektiva symptom.

Syfte

Det övergripande syftet med denna avhandling var att undersöka i vilken omfattning patienter med SLE rapporterar sjukdomsrelaterad smärta och hur smärtan påverkar hälsan och olika aspekter i vardagslivet.

I delarbete 1 var syftet att undersöka intensiteten och karaktären på den smärta som patienten själv relaterar till SLE samt hur sjukdomsaktiviteten och sjukdomsdurationen förhåller sig till smärtan.

I delarbete 2 var syftet att undersöka intensiteten av all slags smärta, hälso-relaterad livskvalitet, trötthet, oro och nedstämdhet hos patienter med SLE och jämföra med ålders- och könsmatchade kontrollpersoner från befolkningen.

I delarbete 3 var syftet att undersöka intensiteten av SLE-relaterad smärta efter sju år, förekomst av långvarig utbredd smärta, hälso-relaterad livskvalitet, trötthet samt oro och nedstämdhet.

I delarbete 4 var syftet att undersöka hur SLE-relaterad smärta påverkar patienternas vardag samt vilket stöd patienterna ansåg sig behöva från vårdgivare för att bättre hantera smärtan.

Deltagare och metod

Vid den första datainsamlingen (år 0), som utgörs av delarbete 1 och 2, deltog 84 patienter med SLE och 91 köns- och åldersmatchade kontrollpersoner slumpvis utvalda från befolkningen. Deltagarna rekryterades från en större pågående studie, SLEVIC (SLE Vascular Impact Cohort), där hjärt- och kärlsjukdomar hos patienter med SLE undersöktes. Deltagarna fick fylla i självskattningsformulär om hur intensiv de upplevde att smärtan varit under den senaste veckan och om hur de upplevde hälso-relaterad livskvalitet, trötthet, oro och nedstämdhet.

De självskattningsformulär som användes var:

Visuell Analog Skala (VAS) användes för att mäta intensiteten av SLE-relaterad smärta under den senaste veckan. Skalan består av en 100 mm lång horisontell linje med två ändpunkter: "ingen smärta" och "värsta tänkbara smärta". Studiedeltagarna fick markera den upplevda smärtan med ett lodrätt streck över den horisontella linjen.

Short-Form McGill Pain Questionnaire (SF-MPQ) användes för att mäta intensiteten och karaktären på smärtan den senaste veckan utifrån 15 fördefinierade beskrivande ord. Formuläret innehåller även en VAS-skala där deltagarna fick skatta sin aktuella smärta samt ett avsnitt där deltagarna fick beskriva sin nuvarande smärta utifrån fördefinierade beskrivande ord.

Medical Outcomes Survey-Short Form 36 (SF-36) användes för att mäta hälso-relaterad livskvalitet. Formuläret består av 36 frågor där svaren sammanställs i åtta dimensioner av hälso-relaterad livskvalitet.

Multidimensional Assessment of Fatigue (MAF) användes för att mäta trötthet under den senaste veckan. Formuläret mäter trötthet utifrån fyra dimensioner: svårighetsgrad, graden av

problem, graden av påverkan på det dagliga livet och tidsperspektivet.

Hospital Anxiety and Depression Scale (HADS) användes för att mäta symptom på oro och nedstämdhet. Formuläret består av 14 frågor, där sju frågor sammanställs till ett index för oro och de andra sju frågorna till ett index för nedstämdhet.

Dessutom insamlades data om ålder, sjukdomsduration, sjukdomsaktivitet (SLAM och SLEDAI), SLE skadeindex (SLICC) samt behandling med kortison.

Vid sju-års-uppföljningen (år 7), som utgörs av delarbete 3, deltog 64 patienter med SLE och 68 kontrollpersoner från samma grupp av deltagare som medverkade år 0. I denna sju-års-uppföljning insamlades data som vid år 0 och deltagarna fick återigen fylla i samma självskattningsformulär. Som tillägg vid år 7 fick deltagarna på en VAS-skala (100 mm) skatta graden av problem som smärtan förorsakat, samt hur länge smärtan hade förekommit. Om smärtan varit närvarande mer än tre månader fick deltagarna också markera på en kroppsschablon vilka kroppsdelar som gjorde ont

I delarbete 4 blev 20 patienter med SLE och sjukdomsrelaterad smärta intervjuade om hur de upplevde smärtan, hur den påverkade deras vardagsliv och vilket stöd från vårdgivare som de ansåg sig behöva för att bättre hantera smärtan. Intervjuerna genomfördes individuellt med hjälp av en intervjuguide och spelades in. De inspelade intervjuerna transkriberades ordagrant och texten analyserades med kvalitativ innehållsanalys.

Samtliga delarbeten i denna avhandling har blivit godkända av den regionala etikprövningsnämnden i Stockholm. Samtliga deltagare lämnade skriftligt informerat samtycke till deltagandet.

Resultat

Vid analysen av rapporterad smärtintensitet på VAS år 0 kunde patienterna delas in i två grupper som skilde sig signifikant från varandra i rapporterad smärtintensitet på VAS: patienter som rapporterade låg grad av smärta, <40 mm på VAS, (64 st) och patienter som rapporterade hög grad av smärta, ≥ 40 mm på VAS, 24% (20 st). Patienterna med hög grad av smärta karaktäriserades av högre sjukdomsaktivitet och kortare sjukdomsduration jämfört med patienterna med låg grad av smärta. I delarbete 2 rapporterade patienterna med hög grad av smärta sämre hälso-relaterad livskvalitet, mer trötthet, oro och nedstämdhet. Patienterna med låg grad av smärta skilde sig inte signifikant från kontrollpersonerna beträffande smärta, i dimensionerna fysisk roll, kroppslig smärta, känslomässig roll och mental hälsa i SF-36 (hälso-relaterad livskvalitet) samt beträffande trötthet, oro och nedstämdhet.

Vid år 7 bibehölls gruppindelningen av patienterna som gjordes utifrån rapporterad smärtintensitet vid år 0. Det innebar att vid år 7 ingick 50 patienter i gruppen med låg grad av

smärta och 14 patienter med hög grad av smärta. De patienter som rapporterade låg grad av smärta vid år 0, rapporterade statistiskt oförändrad smärtintensitet, oförändrad hälso-relaterad livskvalitet (förutom i dimensionen fysisk funktion) samt oförändrad skattning av trötthet, oro och nedstämdhet vid år 7. Patienterna med hög grad av smärta vid år 0 skattade signifikant lägre grad av smärta vid år 7. Dock visade det sig att det bara var hälften (sju patienter) som hade uppnått en tydlig förbättring medan resterande sju patienter skattade statistiskt oförändrad smärtintensitet. Patienterna med minskad smärta skattade även signifikant bättre hälso-relaterad livskvalitet samt mindre trötthet, oro och nedstämdhet. Omvänt skattade patienterna med kvarstående hög grad av smärta oförändrad och sämre hälso-relaterad livskvalitet, mer trötthet, oro och nedstämdhet jämfört med de övriga patienterna och kontrollpersonerna. Samtliga patienter med kvarvarande hög grad av smärta rapporterade långvarig utbredd smärta.

I delarbete 4 berättade informanterna om smärtan som de själva relaterade till SLE, även om de ibland blev osäkra på orsaken till smärtan. De beskrev smärtan som långvarig och ständigt närvarande men på olika ställen. Smärtan och tröttheten var beroende av varandra och förstärkte varandra. Många känslor, framförallt frustration, ilska och sorg triggades av smärtan. Smärtan väckte också existentiella tankar om hur och varför livet med smärta hade blivit som det blev. Mer eller mindre hade informanterna funnit en acceptans och försökte anpassa sig till sjukdomen och smärtan. Att vara sjuk betraktades av informanterna som något annat än SLE, t.ex. som en influensa eller en förkylning.

Smärtan var ett hinder för informanterna att vara fysiskt aktiva i den utsträckning som de ville och att utföra praktiska sysslor i det dagliga livet. Dessutom påverkade smärtan även relationerna till andra och kunde försvåra för informanterna att bibehålla sina olika roller. För att hantera smärtan använde informanterna sina inre resurser som t.ex. viljestyrka, envishet och anpassning. Även praktiska handlingar, fysisk aktivitet, hjälpmedel och läkemedel användes, men trots deras försök att lindra smärtan medförde detta sällan fullständig smärtfrihet.

Trots smärtans negativa påverkan kunde informanterna berätta om att deras erfarenheter av smärta hade bidragit till självutveckling såsom inre styrka, att uppskatta andra och nya aspekter i livet samt en ökad förståelse för andras svårigheter.

Informanterna berättade om sina erfarenheter av bra och empatiskt bemötande i vården men också om dåligt bemötande och misstroende från vårdgivare. Berättelserna betonade att ett gott bemötande och bekräftelse av smärtan från vårdgivare var av avgörande betydelse för hur informanterna upplevde stödet från vården. Individuellt anpassat stöd, kunskap och information om SLE och smärta efterfrågades från vården liksom god tillgänglighet genom

alternativa kommunikationsvägar. Behovet av strukturella och organisatoriska förändringar lyftes av informanterna för att de själva inte skulle vara en budbärare i den egna vården. Förhoppningar fanns om att olika åtgärder och behandlingar liksom behövliga hjälpmedel inte skulle vara beroende av den enskildes ekonomiska situation.

Konklusion

Resultaten från dessa studier visar att patienter med SLE inte är en enhetlig grupp beträffande sjukdomsrelaterad smärta utan att smärtan förekommer i olika utsträckning hos olika individer och över tid. Majoriteten av patienterna rapporterade låg grad av smärta och skilde sig inte i någon högre grad från befolkningen i övrigt beträffande hälso-relaterad livskvalitet, trötthet, oro och nedstämdhet. Dock, den mindre andel av patienterna som hade hög grad av smärta rapporterade avsevärt försämrad hälso-relaterad livskvalitet, mer trötthet och större hinder i det dagliga livet. Trots låg sjukdomsaktivitet och frånvaro av allvarliga organengagemang är därför smärta ett viktigt symptom att uppmärksamma i vården av patienter med SLE. Förutom farmakologisk smärtlindrande behandling är få andra interventioner tillgängliga för att lindra smärtproblem hos patienter med SLE. Det behövs därför fortsatt forskning om olika interventioner för att lindra smärtan och stödja patienten. Nätverk mellan olika professioner och vårdgivare bör också utvecklas för att patienter med smärta inte själva ska behöva vara budbärare i sin egen vård. Dock kan mycket göras med nuvarande kunskap och organisation. Att bemöta patienten med respekt och att bekräfta patientens upplevelse av smärta är en förutsättning för att patienter med SLE-relaterad smärta ska uppleva stöd i vården.

16 ACKNOWLEDGEMENTS

First, I would like to express my gratitude to all patients who participated in the studies forming the basis for this thesis. Thank you for generously having shared your time and the experiences of your daily struggles. Your participation has contributed to an improved knowledge of SLE-related pain and to illustrate the impact of SLE-related pain in daily life.

This gain in knowledge can hopefully serve to raise the awareness of pain in SLE and emphasize the importance of developing and implementing individually targeted interventions against pain.

And on a personal note, without your participation, this thesis would not have been possible. Many thanks for participating in this team-work!

Furthermore, I would also like to give my sincere appreciation to all who have contributed to this thesis. In view of the work over several years leading to this thesis, I would in particular give my warm thanks to those enabling the project execution:

Elisabet Welin, my main supervisor, who during my labors with this thesis so tirelessly and optimistically have guided me on this journey, and which now have reached its destination. You have taught me so many things about nursing science and research, and not least to go outside my comfort zone *heja heja*. Many warm thanks for the opportunity to be your PhD-student and for excellent supervision and support. I could not have had a better supervisor than you!

Johan Frostegård, my co-supervisor, for having contributed to this thesis with your expertise in SLE, and for support, and last but not least, for having given me the opportunity to start this project within the SLEVIC study.

Stefan Bergman, my co-supervisor, for having contributed to this thesis with your expertise in the field of pain. Also, many thanks for your valuable advices and supportive feed-back on my manuscripts.

Sofia Ajeganova, my co-supervisor and coworker in the SLEVIC-study, for having contributed with your great knowledge in SLE and in statistics. Thank you for your patience when assisting me with statistical methods in conjunction with the evaluations.

Ann-Charlotte Elkan, colleague and co-supervisor for my licentiate degree, for your collegial support, friendly advice and for having introduced me into statistical methods.

Susanne Petterson, mentor, co-author, colleague and friend, for being a role-model within nursing science and for your helpfulness when I have needed it.

Ingjald Hafström, thank you for having shared your engagement in rheumatology research with me over these years, and for your invaluable contribution to the SLEVIC studies.

Cristina Anania, Margareta Wörnert and Mona Haag-Westvall, my co-workers in the SLEVIC study, for your commitment and cooperation within the study that for me was the starting point of this journey. Thanks for all the funny moments!

Ronald van Vollenhoven, co-author, for having enabled this journey and for having contributed to this thesis with your great experience in SLE and rheumatology research.

Iva Gunnarsson and Elisabet Svenungsson, for so generously having allowed me to share your study data, and for having included me into your scientific club for networking among stakeholders involved in SLE research. You really do a great job for patients with SLE and doctoral students.

Sofia Ernestam and Jennie Sawalha, my chiefs, thank you for your encouragement and for having facilitated my conclusion of this thesis. Also thank you for creating such a wonderful creative workplace.

Jon Lampa, for having invited me to work as research nurse in your research group and for having shared your scientific thoughts about pain. You have not formally contributed to this thesis but my work within your research group have given me knowledges and inspiration in my own work with this thesis.

The network for caring research at the Rheumatology department Karolinska, for interprofessional support and inspiration as well as for creating such an encouraging and allowing atmosphere for scientific ideas and discussions. I look forward to our meetings and discussions.

All my incredible colleagues and co-workers, for making me love my work and for sharing ups and downs. A special thanks to Sofia Geschwind for taking care of our patients when thesis work called. You have all contributed to this thesis by inspiring me with your experienced knowledge and your engagement in patients with different rheumatological diseases. You are the best!

Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Nursing who have given me the opportunity to personal and professional development and

for excellent education. A special thanks to Annica Karlsson who has kept an eye on me and guided the work through its formal requirements.

My family and friends, you have all provided me with love, energy and joys, priceless when challenged myself on this journey. You have been my parachute. I love you!

This work was supported by grants from the Swedish Rheumatism Association, King Gustav V 80-year's Foundation, Linköping University, the Swedish Society of Nursing and through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and the Karolinska Institutet.

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